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CONGENITAL ENCEPHALO-OPHTHALMIC DYSPLASIA

ARLINGTON C. KRAUSE, M.D.
CHICAGO

PRENATAL and neonatal retinopathy with congenital cerebral dysplasia is a rare syndrome. It is believed that the term "congenital encephalo-ophthalmic dysplasia" would be a suitable name for this disease, since chiefly the brain and the retina with their associated structures (but not the spinal cord) are affected by the disease, which has its origin in prenatal life. Parts of the syndrome occurring in a few cases have been described previously, but the disease has not been studied as a general pathologic process and a clinical entity. Various aspects have been presented—the ocular disease by the ophthalmologists, the cerebral dysplasia and hydrocephalus by the neurologists and the blindness and mental retardation by psychologists and psychiatrists.

The disease is characterized by retinal and cerebral hypoplasia and hyperplasia. The ocular disease is made manifest by the secondary changes; these include microphthalmos; malformations of the retina, choroid and optic nerve; retinal dysplasia; retinal glial membranes, cones and septums, and persistent remains of the hyaloid artery. Retinal detachment is associated with the same process which causes retinal dysplasia. The secondary effects are retinal atrophy, gliosis, fibrosis, intraocular hemorrhages and exudates, secondary glaucoma, atrophy of the iris, anterior and posterior synechias, cyclitic membranes, choroidal and scleral atrophy and cataracts.

The cerebral dysplasia is shown by the heterotopias and the hyperplasia, hypoplasia and aplasia of the cerebrum and the cerebellum. The secondary effects are the hydrocephalus, arising from the cerebral and arachnoidal dysplasia, and the microcephaly, reflected from the microencephaly resulting from the cerebral and cerebellar agenesis.

The syndrome is sometimes cryptic and is not always complete. The signs of the disease may be hidden at birth. The ocular disease may become evident later, but only on close examination. Clinically, the

From the Division of Ophthalmology, Department of Surgery, University of Chicago.

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ocular symptoms are usually easily discovered several months after birth, but the cerebral signs are not so evident unless the child has definite cerebral agenesis or hydrocephalus or later shows pronounced mental retardation not related to loss of vision. Apparently, the mildest forms of the ocular disease may occur as a small area of retinal atrophy or as a slight structural anomaly of the eye; the mildest cerebral disease may be an unrecognizable, slight cerebral dysplasia. Clinically, the disease may affect only the eye, or perhaps only the brain. One part of the syndrome may be observed clinically, and the other part may be discovered at autopsy. In the severe form of the disease the infant may have early fetal hydrocephalus and detached, dystrophic retinas and may die in utero.

HISTORICAL SURVEY

Retrolental Fibroplasia.—The 18 cases of congenital encephalo-ophthalmic dysplasia in this study are similar to or identical with Terry's cases reported under the title of fibroplasia.[1] The best definition of the term was given in 1944,[1e] when he stated:

> The development of embryonic connective tissue in the meshwork of the persistent hyaloid artery system behind the crystalline lens as a result of improper development of the inner eye, usually developing 3 to 5 months after birth in the extremely premature infant, is a disease entity which I call "retrolental fibroplasia."

Terry's first 6 cases[1b] were those of infants from 6 to 7 months of age with symptoms of blindness, nystagmoid movements and squint, noticed four to six months after birth. The children were born prematurely after twenty-seven to thirty-six weeks' gestation, with weights at birth of from 907 to 1,673 Gm. The eyes showed nystagmoid movements, a shallow anterior chamber and a gray pupillary reflex due to a retrolental mass, which presumably was derived from mesodermal tissue. Both eyes were involved in all cases. In 1 eye a small area of chorioretinal atrophy was observed. In another eye the gray reflex, or membrane, was incomplete nasally, so that the fundus was seen.

In 2 cases there were posterior synechias, and in 3 cases the pupils reacted to light. In 3 cases the eyes were small, and in 2 cases a

1. Terry, T. L.: (*a*) Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens, Am. J. Ophth. **25**:203, 1943; (*b*) Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: II. Report of Cases; Clinical Aspects, Arch. Ophth. **29**:36 (Jan.) 1943; (*c*) IV. Etiologic Factors, ibid. **29**:54 (Jan.) 1943; (*d*) Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Infants Born Prematurely: III. Studies in Development and Regression of Hyaloid Artery and Tunica Vasculosa Lentis, Am. J. Ophth. **25**:1409, 1942; (*e*) Retrolental Fibroplasia, Proc. Inst. Med. Chicago **15**:150, 1944; (*f*) Retrolental Fibroplasia in Premature Infants: V. Further Studies on Fibroplastic Overgrowth of Persistent Tunica Vasculosa Lentis, Arch. Ophth. **33**:203 (March) 1945.

hyaloid artery was seen. The seventh, or last, case was that of an infant born only twenty-six days prematurely and weighing 3,421 Gm. at birth. One eye was removed on the basis of a diagnosis of probable retinoblastoma. No hyaloid artery or retrolental fibroplasia was found on pathologic examination. A large cone of glial tissue projected forward from the optic nerve. A few filaments of tissue connected the tip of the cone with the lens and the ora serrata. Later, Terry [1f] omitted the seventh case from this series because the same disease occurred in another child in the family.

Persistent Hyaloid Artery and Fibroplasia.—The question arises whether or not this so-called retrolental fibroplasia is comparable to other cases in the literature in which fibrous tissue was associated with a persistent hyaloid artery. A review of 31 cases [2] collected from the

2. (*a*) Nettleship, E.: Curator's Pathological Report, Ophth. Hosp. Rep. **7**:632, 1875. (*b*) Brailey, W. A.: Curator's Pathological Report, ibid. **8**:543, 1876. (*c*) Gardiner, E. J.: A Case of Persistent Hyaloid Canal and Artery, Arch. Ophth. **9**:473, 1880. (*d*) de Wecker, cited by Gardiner.[2e] (*e*) Vassaux, G.: Persistance de l'artère hyaloidienne et de la membrane pupillaire, ayant determiné des altérations intra-oculaires, simulant cliniquement un néoplasme, Arch. d'opht. **3**:502, 1883. (*f*) Snell, S.: Congenital Defects, Tr. Ophth. Soc. U. Kingdom **4**:349, 1883. (*g*) Hess, C.: Zur Pathogenese des Mikrophthalmus, Arch. f. Ophth. **34**:148, 1888. (*h*) von Grolman, W.: Ueber Mikrophthalmus und Cataracta congenita vasculosa, ibid. **35**:187, 1889. (*i*) Collins, E. T.: On the Development and Abnormalities of the Zonule of Zinn, Ophth. Hosp. Rep. **13**:81, 1892; (*j*) Pseudo-Glioma, ibid. **13**:361, 1892. (*k*) Ridley, N. C., and Marshall, C. D.: Atypical Development of the Vitreous: Persistent Hyaloid Artery, Tr. Ophth. Soc. U. Kingdom **18**:188, 1898. (*l*) Salffner, B.: Bulbus Septatus, Arch. f. Ophth. **54**:552, 1902. (*m*) Parsons, J. H.: Microscopical Section of Pseudo-Glioma Due to Congenital Membrane Behind the Lens, Tr. Ophth. Soc. U. Kingdom **22**:253, 1902; (*n*) Sections from a Case of Microphthalmus, ibid. **22**:258, 1902. (*o*) Fleming, P., and Parsons, J. H.: Persistent Hyaloid Artery, ibid. **23**:242, 1903. (*p*) de Vries, W. M.: Ueber eine Mi.sbildung des menschlichen Auges (Coloboma iridis, Katarakt, Stränge und Gefässe im Glaskörper), Arch. f. Ophth. **57**:544, 1904. (*q*) Collins, E. T.: Developmental Deformities of the Crystalline Lens, Tr. Sect. Ophth., A. M. A., 1908, p. 452. (*r*) Fibrous Tissue Formation, Tr. Ophth. Soc. U. Kingdom **33**:173, 1913. (*s*) Howard, H.: Multiple Congenital Abnormalities of the Eye, Tr. Am. Ophth. Soc. **15**:244, 1917. (*t*) Lane, F.: Fibrovascular Sheath of the Lens, Arch. Ophth. **48**:572, 1919. (*u*) Lent, E. J., and Lyon, M. B.: Fibrovascular Sheath of the Crystalline Lens, Am. J. Ophth. **5**:706, 1922. (*v*) Gifford, S. R.: Pseudoglioma and Remains of the Tunica Vasculosa Lentis, ibid. **6**:565, 1923. (*w*) Lloyd, R. I.: Pseudoglioma, ibid. **14**:27, 1931. (*x*) Pollack, W. B. I.: Case of Pseudoglioma, Tr. Ophth. Soc. U. Kingdom **43**:263, 1923. (*y*) Holmes, E. L.: A Case of Persistent Hyaloid Canal, Arch. Ophth. **10**:168, 1881. (*z*) Clarke, E.: Pseudoglioma in Both Eyes, Tr. Ophth. Soc. U. Kingdom **18**:130, 1898. (*a'*) Rockliffe, W. C.: Pseudoglioma, ibid. **18**: 139, 1898. (*b'*) Galloway, N. P. R.: Bilateral Pseudoglioma, ibid. **52**:553, 1922. (*c'*) Heine, L.: Ueber das familiäre Auftreten von Pseudoglioma congenitum bei

(Footnote continued on next page)

literature in which a clinical diagnosis of persistent hyaloid artery had been made revealed the following grouping: (1) 1 case of metastatic ophthalmitis, which may be discarded; (2) 2 clinical cases without postlental fibrous tissue, in 1 of which a persistent hyaloid artery only was seen and in the other a network of vessels lay on the posterior capsule; (3) 2 clinical cases in which a white reflex was seen unilaterally; (4) 3 clinical cases with a posterior polar cataract and a hyaloid artery; (5) 3 clinical cases with a gray mass in the pupil, which on removal showed retrolental fibrous tissue but no hyaloid artery, and (6) 20 cases with a gray pupillary reflex, retrolental fibrous tissue and a persistent hyaloid artery.

The 26 cases of the last three groups may be classified under retrolental fibroplasia with a persistent hyaloid artery and are taken for analysis. The symptoms were blindness, nystagmoid movements and a white pupillary reflex. Prematurity was not mentioned. It is remarkable that in every case the lesion was unilateral. The anterior chamber was observed to be shallow in 11 cases, and posterior synechias were present in 10 cases. In 16 cases the symptoms pertaining to the abnormal eye were noticed before the age of 6 months. In 20 cases a preoperative diagnosis of retinoblastoma was made. Associated nonocular conditions in these cases were not mentioned or are not pertinent to this discussion.

Of the group, all but 3 eyes were removed. Microphthalmos was evident in 12 eyes. Retrolental fibrous tissue and the hyaloid artery were shown in histologic sections in 23 eyes. In only 4 eyes was retinal detachment observed. Of these, the retina was detached nasally in 1 eye; in another it was detached eight years after the first ophthalmic examination, and in the other 2 eyes the retinas are described simply as detached by "albuminous material."

Thus it may be seen clinically that the disease called retrolental fibroplasia by Terry and the disease designated in the literature as connective tissue hyperplasia associated with a persistent hyaloid artery are apparently different conditions. They have the following signs in common: gray pupillary reflex, shallow anterior chamber, posterior synechias and microphthalmos in the newborn. Retrolental fibroplasia is bilateral and usually appears in premature infants. In the second disease, on the contrary, the hyperplastic mass associated with the persistent hyaloid artery is unilateral and is not related to prematurity. Vision in the other eye is generally good. The 18 cases from the Uni-

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zwei Brüdern und Amotio retinæ acq. bei Vater und Sohn und über Pseudogliom mit Nekrose der Uvea und Retina beim Sohn eines Vaters mit Iritis, Ztschr. f. Augenh. **56**:155, 1925. (*d'*) Lachman, G. L.: Bilateral Hemorrhagic Detachment of Retina in New Born Simulating Glioma, Am. J. Ophth. **10**:164, 1927. (*e'*) Wetzel, J. O.: Pseudoglioma of the Retina, ibid. **24**:164, 1941.

versity of Chicago Clinics presented in this paper are similar clinically to the cases reported by Terry, but they cannot be regarded as instances of retrolental fibroplasia associated with a persistent hyaloid artery.

Encephalic Dysplasia.—As far as I am able to determine, there are few cases of encephalic dysplasia reported in the literature which may be considered as coming under the classification of congenital encephalo-ophthalmic dysplasia. In a recent clinical case of retinal folds [3] the lesion was reported to be associated with microcephaly and mental retardation, and in another clinical case [4] a retinal fold occurred in one eye and a retinal detachment in the other. In at least 2 of the 5 cases [5] with lissencephaly there was no pupillary reaction to light. In the 1 case in which ophthalmoscopic examination was made no abnormality was visible.

A complete description of a patient having cerebral and retinal dysplasia was given by Wehrli.[6] The infant was delivered fourteen days prematurely with instruments because the membranes were ruptured. The other twin survived and remained healthy. The patient died at the age of 16 months of gastroenteritis. At autopsy the eyes were observed to be normal in size. The left eye was removed because ophthalmoscopic examination showed a small nodule in the retina near the disk. The fundus of the other eye appeared normal. Pathologic examination of the left eye revealed pronounced hypoplasia of the retina. The stratified layers were thin, and the cells were few and small. The hypoplasia affected mainly the outer neurons. The small tumor was composed of a double inner nuclear layer and many incompletely differentiated retinal cells, superimposed on an abnormally thin retina peripherally. Beneath the tumor the retina was irregular and distorted. The rest of the eye was normal. The child was hydrocephalic. The brain showed microgyria, macrogyria, heterotopias and small embryonal tumors of the ependyma. The spinal cord was normal. The disease in this case was like that in cases 9 and 10 of the present series.

REPORT OF CASES

Over sixty physicians have aided in the study of these cases. Without the assistance of Dr. Douglas N. Buchanan, of the department of pediatrics, and Miss Miriam Norris, in the social service department of the University of Chicago, this study could not have been completed.

3. Gartner, S.: Congenital Retinal Folds and Microcephaly, Arch. Ophth. **25**:93 (Jan.) 1941.

4. Guerry, D.: Congenital Retinal Folds, Am. J. Ophth. **27**:1132, 1944.

5. Walker, A. E.: Lissencephaly, Arch. Neurol. & Psychiat. **48**:13 (July) 1942.

6. Wehrli, E.: Ueber der Mikro- und Makrogyrie des Gehirnsanaloge Entwicklungsstörungen der Retina mit Besprechung der Epithelrosetten und der Pathogenese des Glioma, Arch. f. Ophth. **60**:302, 1905.

All patients were repeatedly seen by me except for the eighth, who died twenty-four hours after birth. The eyes were usually examined while the child was under general anesthesia. In many cases the biomicroscope was employed.

CASE 1.—M. L., a white girl, was delivered by cesarean operation in the University of Chicago Clinics on Oct. 29, 1937, after six and one-half months' gestation because the mother had toxemia of pregnancy. The placenta and uterus of the mother were normal microscopically. The weight of the child was 900 Gm., and the length was 37 cm. The circumference of the head was 35.6 cm. No physical abnormalities were found on examination. The child was kept in an incubator for three weeks and was treated for weakness and anemia in the hospital until Jan. 6, 1938. On discharge she was in good health and weighed 2,495 Gm.

The father and mother were born in the Netherlands. The father, aged 41, had hypertensive heart disease. The mother, aged 44, had essential hypertension and belonged to a family with a tendency toward essential hypertension. Her fundi were normal in appearance after delivery. The patient was the result of a second pregnancy; the first child, a girl, was 18 years of age and healthy. No evidence of ancestral nervous or ocular disease was obtainable.

On April 27, 1938 the mother returned with the child to the University Clinics. When she had arrived home, she had incidentally noticed that the child, at the age of 9 weeks, was unable to see objects, but squinted, in bright sunlight. Examination by the pediatrician showed that the child, a small, premature infant, was normal except for the eyes. The blood count and urine were normal. The Wassermann reaction of the blood was negative. The child was referred to the eye clinic.

The eyes gave no reaction to light. Searching nystagmoid movements were observed. The external ocular movements were unrestricted. The lacrimal apparatus, lids and conjunctiva were normal. The right cornea was 9 mm., and the left 9 mm., in diameter. The anterior chambers were shallow. The pupils were dilated and fixed. A greenish mass, which was derived from the retina, was seen back of each pupil. The tactile tension of the right eye was moderately higher than normal, and that of the left eye was normal. A diagnosis of bilateral retinoblastoma was made. On May 3, 1938 the right eye was removed.

On May 19 examination of the left eye showed a collapsed anterior chamber, new vessels on the anterior surface of the iris, posterior synechias, a vascularized mass in contact with the posterior surface of the lens and a high tactile intraocular tension. On May 21 the left eye was removed.

On Oct. 22, 1940 mental retardation was noticed. The Kuhlmann psychometric test gave an intelligence quotient of 41. Vocabulary and memory were poorly developed.

In December 1940, according to the report of another institution, two psychologists and a psychiatrist found the child well and not physically handicapped or mentally retarded except for what could be ascribed to the loss of sight, as determined by informal examinations. The weight was 10.9 Kg., and the circumference of the head was 47.5 cm.

According to the statement from the county coroner's physician, the child died on Feb. 27, 1941, of a mass in the brain. The diagnosis was not specific but was indicative of cerebral disease or hydrocephalus.

Pathologic Examination.—Right Eye (fig. 1*A*): The ocular bulb displaced 2.25 cc. of 4 per cent alcohol. The diameter of the bulb was 15.5 mm. antero-

posteriorly and 15.5 mm. transversely. The diameter of the cornea was 9 mm. The depth of the anterior chamber was 0.4 mm. The filtration angle was partly open. The canal of Schlemm was small and multiple channeled. The choroid and the sclera were normal. About one third of the posterior pigment layer of the iris around the pupil was adherent to the anterior capsule of the lens. The lens was normal. Remains of an embryonic vascular system around the lens were not present. Just behind the lens a few amorphous strands of vitreous were seen to fray out laterally and to extend as fibrils to the ciliary body and processes. The space posterior to this was quite empty, and only one or two capillaries were present in the central serial sections.

On the inner surface of the pigment epithelium of the retina occasional small clumps of proliferating pigment cells and many ghost cells were seen. In the macular region the ghost cells were fifteen cells deep in one small area. The retina was detached in an area extending from the disk to the ciliary body.

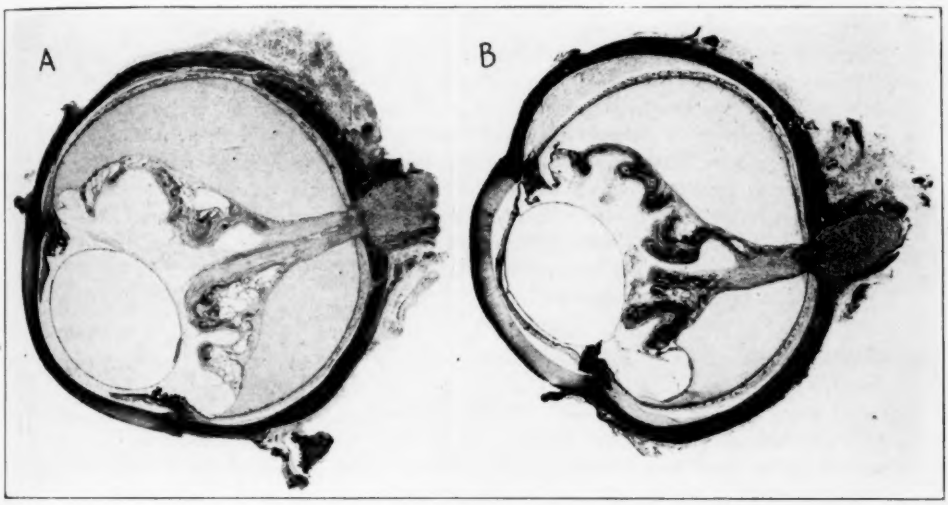

Fig. 1 (case 1).—Cross sections of (*A*) the right eye and (*B*) the left eye. The lower part of *B* is the nasal side. × 4.

The retinal mass had the shape of a blunt funnel. The stem leading from the optic nerve was not completely closed and was walled with the nerve fibers. The retinal vessels were in the middle of the stem. The peripheral tissue of the anterior part of the detached, atrophic, lobulated retina consisted of a layer of irregular neuroepithelium. In the lobules of the retina were many large, empty cystic spaces, the largest of which was about 2 mm. in diameter. Scanty stratification of a few layers was noticeable in the disorganized, distorted retinal tissues. Several nests of pigment epithelial cells were noted externally on the posterior surface of the retina. The space between the pigment epithelium and the detached retina was filled with a serous exudate. A few lymphocytes were scattered throughout the retinal mass.

The optic nerve fibers were myelinated.

Left Eye (fig. 1*B*): The bulb displaced 2.5 cc. of 8 per cent alcohol. It measured 15 mm. anteroposteriorly and 15.5 mm. transversely. The diameter of

the cornea was 9.5 mm. The filtration angle was partly open. The canal of Schlemm was patent. The anterior chamber was absent centrally and was 0.4 mm. deep peripherally. The sclera was normal. About one half of the pigment epithelium of the pupillary part of the iris was adherent to the anterior surface of the lens. The central part of the pupillary space was filled with proliferating pigmented and unpigmented epithelial cells, corneal endothelial cells and connective tissue cells, which were adherent to the lens and to Descemet's membrane. The lens was normal. No vessels were seen on or around the lens. A serous exudate infiltrated the outer layers of the anterior half of the choroid. The retinal pigment epithelium was slightly irregular. A layer of ghost cells 20 to 200 microns thick and occasional small, proliferating nodules of pigment epithelial cells, sometimes surrounding a hyaline center, were lying on the inner surface.

The retina was detached from the disk to the first ciliary process. It was shaped like a short funnel. The central stalk was walled with partly organized retina, which surrounded the retinal vessels. No hyaloid artery was evident. The main mass of retina was lobulated by fusion. The lobule nasally possessed a thin glial wall, which was several cells thick. A few large cystic spaces, filled with areolar connective tissue, were present. On the temporal side the retina was fused to the first posterior ciliary processes. The atrophic retina showed irregular stratification, microcysts, pseudorosettes and tubes of cells. Just behind the posterior pole of the lens was an exceedingly thin, transverse, stratified connective tissue membrane, which frilled out laterally to join the retina, the ciliary body and the ciliary processes. Several very small vessels and capillaries were seen in the areolar tissue behind the membrane. An occasional lymphocyte and round cell were present in the retina.

The optic nerve was medullated.

Case 2.—D. S., a white boy, was born at the end of twenty-eight weeks' gestation, after a premature rupture of membranes, on July 10, 1939 in the University of Chicago Clinics. The mother, aged 31, was a primipara. No instruments were used in the delivery. The placenta was normal. The infant was in good condition. No signs of trauma, hemorrhage or other abnormalities were present. The child was placed in an incubator. On the eleventh day of life his weight was 955 Gm. He had no cyanosis, jaundice or convulsions. On discharge from the hospital, on September 19, the child weighed 2,535 Gm. and was healthy.

The father was well, but his age was not obtained. The relatives and ancestors were free of ocular and nervous diseases.

On October 24 the child was examined in the pediatric clinic and was found to be normal for a premature infant.

On December 7 a gray mass was visible through the pupil of each eye. Physical examination showed no abnormalities except for the eyes. The blood count and the urine were normal. The Wassermann reaction of the blood was negative. The patient was referred to the eye clinic.

On December 13 an ophthalmic examination was made. No measurement of vision was obtainable. Bright light produced no blinking or movement of the eyes. Externally the eyes were normal. No restriction of action of the external ocular muscles was evident. The corneas were 9.5 mm. in diameter.

The right cornea showed discrete, gray, deep opacities, 1 to 2 mm. in diameter, distributed in seven loci equidistant rfom each other at the periphery and in a circle 2.5 mm. from the limbus. The superficial reflex was brilliant. The rest of the cornea was clear. No corneal blood vessels or keratitic precipitates were

seen. The anterior chamber was almost obliterated by the blue, thin iris lying against the cornea. The pupillary margin of the iris was ragged and was adherent to the posterior surface of the cornea. No keratitic precipitates or iridic vessels were seen. The pupil was 3 mm. in diameter and was fixed. The lens and the lateral anterior portion of the vitreous were clear. The fundal reflex was gray. An irregular, gray, granular mass, best seen with a + 18 D. lens, filled the posterior part of the vitreous cavity. Two lateral vessels crossed in the mass radially. No details of the mass were observed.

The left cornea, 9.5 mm. in diameter, was clear. The anterior chamber was collapsed. The blue, thin iris was flush against the posterior surface of the cornea. The pupil was 5 mm. in diameter and was fixed to light. No posterior synechias were seen. The lens was clear. A red reflex was obtained nasally at the extreme periphery at 10:30 o'clock. The rest of the fundus was obscured by a yellowish gray mass, which filled the cavum. Several radial vessels in depressions passed to the center of the floating mass. At the periphery of the mass, at 4:30 o'clock, was a small red blood clot, and at 11 o'clock, a group of fine vessels. Only the anterior half of the bulb could be transilluminated. The tension (Souter) was less than 10 mm. in each eye.

A tentative diagnosis of bilateral retinoblastoma was made.

On December 18 the eyes were removed. A course of twenty-four roentgen treatments was given to the orbits for possible extension of growth of the retinoblastomas.

On May 31, 1940 the mother, after twenty-three weeks' gestation, had another premature infant, which was stillborn after premature rupture of the membranes. Histopathologic examination revealed that the infant was a normal, previable fetus with normal eyes.

On May 3, 1943 the psychologists and psychiatrists again examined the patient. No physical or mental abnormalities except those referable to the eyes were evident. The child was healthy and was becoming well adjusted to other children and to the home. On July 9, 1945 his condition was unchanged.

Pathologic Examination.—Right Eye: The anteroposterior diameter of the bulb was 17 mm. and the transverse diameter 17 mm. The bulb displaced 4 cc. of 1 per cent alcohol. The diameter of the cornea was 9.5 mm. The filtration angle was partly open. The canal of Schlemm was patent. The anterior chamber was 0.5 mm. deep. The sclera was normal. The pigment layer of the iris at the pupillary margin was adherent to the lens capsule. The stromal layer gave off projections one to three cells thick, which passed over the pupil onto the lens. The lens was normal. No vestigial embryonic vessels around the lens were seen. The choroid was engorged. Anteriorly, near the ciliary body, the external lamellas were separated by a serofibrous exudate. The pigment epithelium showed a few minute clusters of proliferating cells on the inner surface. At the equator a patch of ghost cells, 3 mm. in width, was seen on the pigment epithelium.

The retina was detached from the disk to the ciliary body. The stalklike central structure was constricted in the middle. The chief mass of retina was behind the lens and was fused to the posterior ciliary processes. The anterior surface of the mass was 11 mm. in diameter. The branches of the central retinal vessels were enclosed in the stalk. A small part of the atrophic retina was incompletely stratified. A few large and many small tubular pseudorosettes were seen in the posterior half of the retina. A few scattered small masses of red blood cells were present in the retinal strata of one lobule and in a few tubular

pseudorosettes. A few leukocytes, plasma cells and phagocytes were disseminated throughout the atrophic retina. The space between the retina and the pigment epithelium was filled with a serous exudate.

Only a few, fine capillaries were seen in the dense transverse vitreous membranes adherent to the middle of the posterior surface of the lens capsule. Lateral to the band of membranes was an areolar vitreous structure.

The optic nerve was apparently normal.

Left Eye (fig. 2 *A*): The diameter of the bulb was 17.25 mm. anteroposteriorly and 16.5 mm. transversely. The bulb displaced 4 cc. of 1 per cent alcohol. The diameter of the cornea was 9.5 mm. The canal of Schlemm was small and was covered partly by the trabeculae in the incomplete opening of the filtration angle. The anterior chamber was 1 mm. deep. It

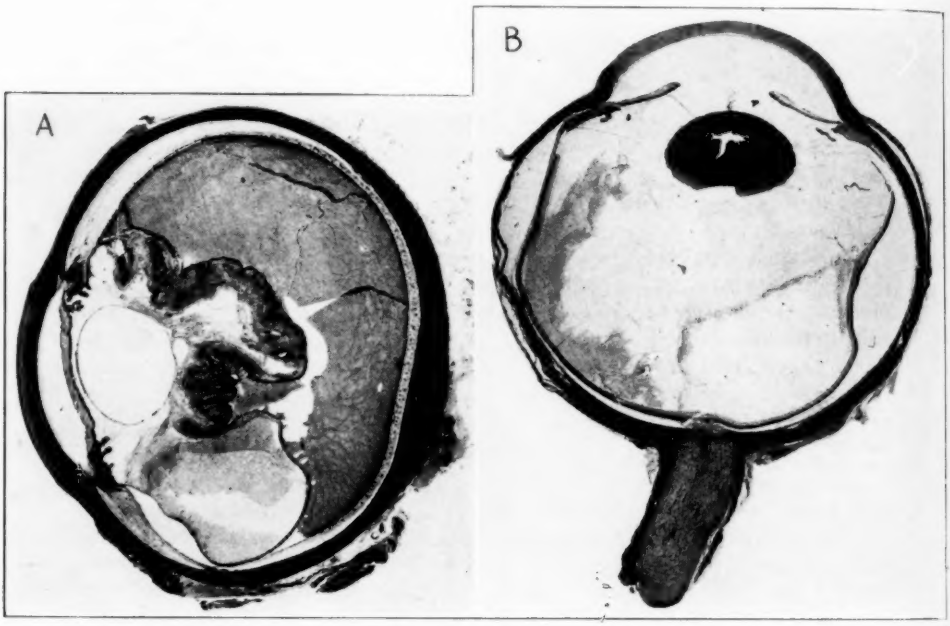

Fig. 2.—*A* (case 2), cross section of the left eye, showing detached retina and large nasal retinal cyst; *B* (case 3), cross section of the right eye. × 4.

contained a small quantity of serous exudate. The sclera was normal. The pupillary pigmented border of the iris was adherent to the anterior capsule. No capillaries and cellular veils were seen on the lens. The lens was normal. The muscle fibers of the ciliary body were not quite completely developed in numbers and in position. The external lamellas of the choroid adjacent to the pars plana contained a serofibrinous exudate. The retinal pigment epithelium showed a few small nodules of proliferating pigment cells. An occasional ghost cell was close to the pigment epithelium. The space between the retina and the pigment epithelium was filled with a serous exudate.

The flower-shaped mass of retina was detached from the disk to the first ciliary process. The main mass of the retina was behind the iris and the lens and was focused laterally to the pars plana. The posterior part of the central

stalk contained the retinal vessels, optic nerve and glial fibers. The anterior mass of retina was lobulated by fusion. Several large lobules were stratified, but the others were irregular masses of retinal cells and glial tissue. A few pseudorosettes and tubules of stratified retinal cells were seen. Microcysts in the masses of cells were present. A dense and layered amorphous membrane covered the posterior central third of the lens capsule. Laterally the membrane fused with areolar tissue and posteriorly with glial tissue. Only a few capillaries were evident in the tissue next to the lens. The retinal mass possessed no large vessels. A part of the retina, forming a sac 6 mm. in diameter, projected nasally and posteriorly from the central postlental retinal mass. The unorganized, atrophic retina and glial tissue formed the thin wall of a cyst, containing a serous fluid. The outer part was fused to the choroid for 4 to 6 mm.

The optic nerve was apparently normal.

CASE 3.—R. R., a white boy, was born in the University of Chicago Clinics on Feb. 23, 1943, after thirty-one weeks' gestation, of a first pregnancy. The placenta was normal. The cause of prematurity was unknown. The other infant of the twin birth died forty-eight hours after delivery.

The child was in good condition and showed no evidence of traumatic injury. He required no artificial revival. The eyes appeared to be normal. The child was placed in a Hess bed with a constant supply of oxygen. At the age of 13 days he weighed 1,100 Gm. During the first three months of life he barely survived infections of the skin, bilateral otitis media and repeated attacks of cyanosis. The infections were treated with sulfathiazole and sulfadiazine. He was discharged from the hospital on May 4, 1943, with a weight of 3,000 Gm. and with a diagnosis of hemangioma of the occiput, systolic cardiac murmur and congenital umbilical hernia.

The father, aged 21, and the mother, aged 20, had always been healthy. Both parents were born in Chicago. Their families had no hereditary ocular or nervous diseases. The Wassermann reaction of the mother was negative.

On May 27 the child was returned to the pediatric clinic, where the pediatrician made a diagnosis of anemia, incipient vitamins C and D deficiency and a mass in the left ocular fundus.

Ophthalmic Examination.—On May 28 an ophthalmic examination was made, although the mother noticed nothing unusual about the child's eyes. Externally the eyes were normal. The corneas were clear.

Right Eye: The anterior chamber was of normal depth. The pupil was round, regular and reactive to light. The lens was clear. The fundus showed a pronounced anomalous distribution of the retinal blood vessels. The vessels seemed to be almost entirely on the temporal side of the disk. The retina had the abnormal color of pink porcelain. The macular reflex was absent.

Left Eye: The anterior chamber was shallow. The pupil was fixed by irregular posterior synechias. Homatropine dilated the pupil irregularly. The lens was clear. The retina was detached and floated as a billowy, vascular gray cloud just behind the lens. A tentative diagnosis of retrolental fibroplasia of the left eye was made.

On June 4, 1943 the child died, while he was on the way to the hospital. He weighed 2,930 Gm.

The pathologic diagnosis was acute enteritis, emaciation, umbilical hernia and small hemangioma of the scalp. The brain weighed 433 Gm. and was normal histologically. The eyes were studied separately.

Histologic Examination.—Right Eye (fig. 2*B*): The anteroposterior diameter of the eye was 16 mm. The cornea was 8.5 mm. in diameter and was normal. The sclera appeared normal. The anterior chamber was 2 mm. deep. The trabeculae partly filled the filtration angle. The pupil was 3 mm. wide. A few cells of the pigmentary border of the pupil were adherent to the anterior surface of the capsule. The lens was normal. No evidence of embryonic vascular structure was seen in the iris or the lens. The ciliary body was normal.

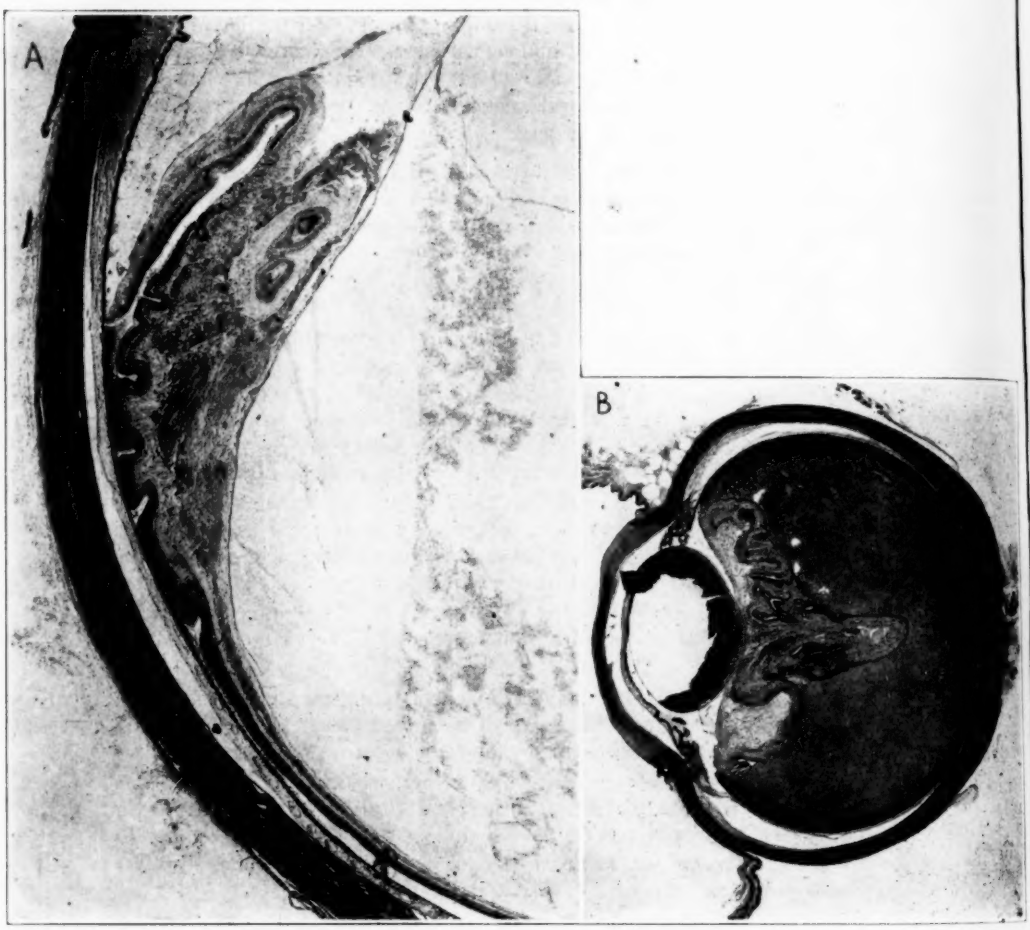

Fig. 3 (case 3).—*A*, cross section of the retina near the ora serrata, showing hyperplasia on the nasal side of the right eye; *B*, cross section of the left eye (× 4).

In one segment nasally, beginning 3 to 4 mm. from the ora serrata, the retina projected as a plicated, unorganized growth, extending from the ora serrata toward the lens in the shape of a half-moon, with the convexity outward (fig. 3*A*). The mass was 8 mm. wide and 2 mm. thick. The double internal limiting membrane of the retina joined the zonular ligaments. The central parts of the folds, where

the retina was detached, were filled with an albuminous fluid. The retina was arranged in stratified and unstratified nodules, tubes and rosettes of cells of the neuroepithelium. Large areas of proliferating neuroglia were seen.

The retina adjacent to the overgrown portion of the retina for about 6 mm. showed multiple, irregular-sized spaces between the cells of the inner and the outer nuclear layer. Below the middle of this area of the retina, the choroid showed conspicuous round cell infiltration. In the center, 2 mm. of the retina was detached and elevated as a mound, over an albuminous fluid. Many scattered red blood cells and a few lymphocytes and macrophages were seen above the pigment epithelium

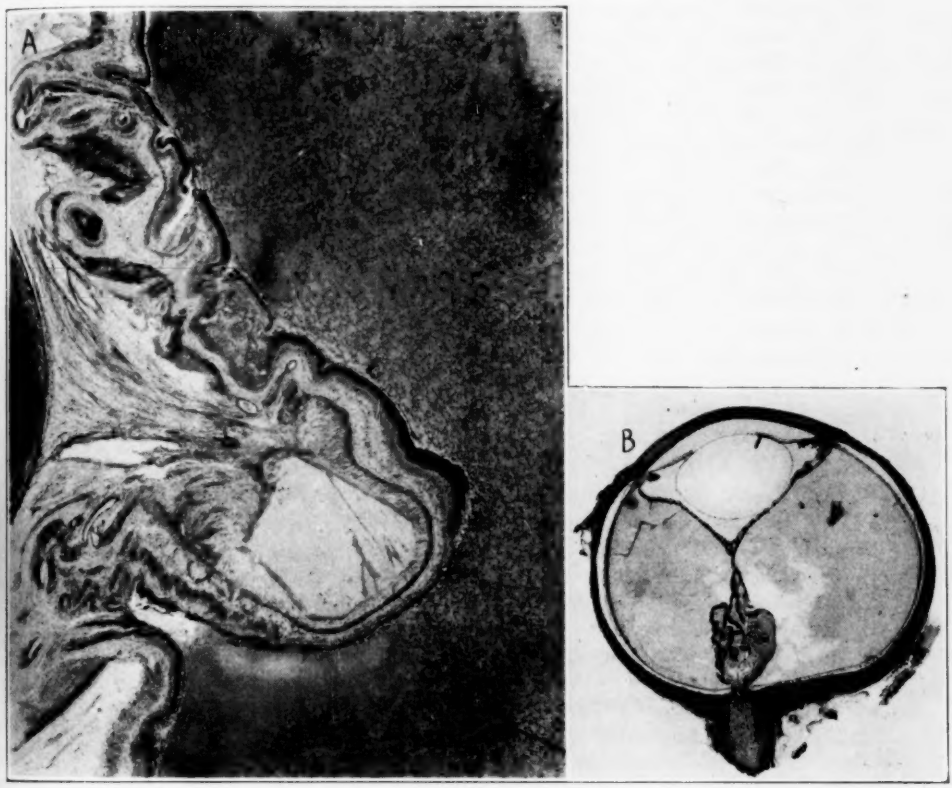

Fig. 4.—*A* (case 3), cross section of the left eye behind the lens, showing absence of hyaloid system and of the postlental mesodermal fibrosis; *B* (case 6), cross section of the left eye (× 3½).

in the fluid. The retina above was thickened chiefly by the large amount of glial cells and fibers. The inner and outer layers of nuclei were irregularly arranged. The nuclei were filled with fine granules. The nuclei were fewer and were spaced so as to show many varied, noncystic gaps. The nerve fiber layer of most of the retina appeared to be thicker and to show more neuroglial nuclei and less ganglionic nuclei than normal. In short, the retina was hypoplastic and hyperplastic. The disk was free from vestigial remains of the hyaloid vascular system. The optic nerve was apparently normal.

Left Eye (fig. 3 *B*): The volume of the bulb was 3.5 cc. The diameter was 15 mm. anteroposteriorly and 15 mm. transversely. The cornea measured 9 mm. vertically and 10 mm. horizontally. The epithelium was thinner in the middle of the cornea. The filtration angle was partly open. The canal of Schlemm was patent. The anterior chamber was 0.5 mm. deep in the center. The sclera was normal. The pigment epithelium of the pupillary border of the iris was adherent to the anterior capsule. A few layers of cells from the stroma of the iris passed onto or over the anterior surface of the lens in the pupillary space. No vessels appeared on the anterior capsule. The choroid was normal. The cells of the pigment epithelium of the retina were slightly pigmented and irregular in size. Many ghost cells were present on the surface of the epithelium.

The retina was detached from the disk to the first ciliary process. It was shaped like a mushroom, with a stalk attached to the optic nerve and with an inverted head lying in contact with the lens, across the anterior portion of the vitreous cavity. The stalk was formed by glia, nerve fibers and a few large vessels. The lobulated retinal mass was formed by fusion of folds of the detached retina. The borders of the lobes were composed of fairly well stratified layers of cells. In one segment of the distorted retina many minute, old hemorrhages and several the size of a pinhead were seen.

Behind the lens was a small, flat mass of vitreous fibrils confluent with glial tissue of the retina. Only a few capillaries were present in the glial or the connective tissue. No embryonic vascular tree or hyaloid artery was seen behind the lens (fig. 4 *A*).

The optic nerve was apparently normal.

Case 4.—M. S., a white girl, was born Dec. 22, 1937, after a gestation of twenty-eight weeks. The cause of the prematurity was unknown. A midwife aided in the delivery. The placenta was not examined. The weight on the sixth day was 1,065 Gm. On the day of birth the infant was admitted to the University of Chicago Clinics with intermittent cyanosis and was placed in an incubator. On Feb. 25, 1938 the infant, healthy and weighing 2,790 Gm., was discharged from the hospital.

The father was 27 and the mother 21. A brother, aged 3 years, and a sister, aged 1 year, were well. On March 26, 1938 the mother brought the child to the University of Chicago Clinics for treatment of a "bulging" left eye, which she had noticed three days before. Physical examination revealed a normal premature child. The circumference of the head was 34 cm. The blood count and the urine were normal.

The conjugate movements of the eyes were normal. The right eye was slightly enlarged. The cornea was clear. The anterior chamber was shallow, particularly on the temporal side. The pupil was oval and irregular. A greenish gray mass, with blood vessels on its anterior surface, was just behind the lens.

The left eye was more prominent and larger than the right eye. The cornea was enlarged and slightly cloudy. The epithelial reflex was dull. The anterior chamber was shallow. The pattern of the iris was blurred. The radial vessels on the iris were engorged. The pupil was irregular and was 5 mm. in diameter. Just behind the lens an irregular, greenish gray mass was seen. The tactile tension was above normal.

A diagnosis of bilateral retinoblastoma was made.

On April 5, 1938 a bilateral enucleation was done. Roentgenologic treatment of the orbits was given.

On Nov. 10, 1942 examination showed definite mental retardation which was not related to loss of vision. The child was well developed but undernourished. She

was unable to use words or to walk unassisted. She was kept under observation until March 13, 1943. On Aug. 15, 1944 she was admitted to an institution for the feebleminded.

Pathologic Examination.—Right Eye: The bulb was 17.5 mm. in diameter anteroposteriorly and 16.5 mm. transversely. The cornea was 10 mm. in diameter. The cornea was thinner than normal. The filtration angle was partly closed as a result of anterior displacement of the peripheral part of the iris. The canal of Schlemm was collapsed. The anterior chamber was shallow. The pupillary part of the iris was adherent to the anterior surface of the capsule. The sclera was thin. The lens was normal. The vessels of the ciliary body, iris and choroid were engorged. Anterior to the equator the choroid was distended by a hemorrhage. On the surface of the retinal pigment epithelium were proliferating pigment cells and ghost cells. The proliferation of neuroepithelial cells tended to fuse the processes together. Anteriorly, double layers of pigment epithelial cells formed large hemorrhagic cysts.

The atrophic retina was detached from the disk to the first posterior ciliary process. The main mass of the retina was shaped like a flower, with a central stalk joining the optic nerve. Small tubes, spheres and layers of stratified retinal cells were present at the periphery of the anterior portion of the retinal mass. Centrally, glial and connective tissue was evident. Posteriorly, the retina was covered with a layer of epithelial and connective tissue cells. Large hemorrhagic cysts were occasionally enclosed. A few leukocytes, plasma cells and phagocytes were scattered throughout the retina. The space between the retina and the epithelial layer was filled with exudate. Posteriorly, the lens capsule was adherent to a thin, transverse, laminated hyaline membrane, the lateral fibrils of which were attached to the ciliary processes and the ciliary body. Posterior to the membrane a small pyramidal space was filled with areolar tissue, which possessed a few capillaries. The stalk consisted of glial and connective tissue, nerve fibers and several large blood vessels. An irregular layer of hyalinized red cells was present beneath the outer wall of the stalk. The interretinal and intraretinal spaces and the anterior and posterior chambers were filled with a hemorrhagic exudate.

The optic nerve was partly atrophied.

Left Eye: The diameter of the bulb measured 19 mm. anteroposteriorly and 16.5 mm. transversely. The diameter of the cornea was 10 mm. The corneal endothelium was flattened. The anterior chamber was 1.8 mm. deep and contained exudate. The sclera was thin. Peripherally, most of the iris touched or adhered to the cornea. The pupillary part of the iris was adherent to the anterior surface of the lens. A serofibrinous exudate, containing erythrocytes, filled the space behind the iris. The lens was normal. The vessels of the choroid and iris were engorged. A large hemorrhage distended the choroid in the region of the ora serrata, where it broke through into the space behind the retina. A few lymphocytes and plasma cells were present in the choroid near the ciliary processes and the pars plana. The pigment epithelium was thickened, multiple layered and distorted over the ora serrata and near the equator. Near the ciliary body it formed strands, islands and cysts in the adjacent retina.

The retina was detached from the disk to the ciliary body. The long, narrow stalk, leading from the anterior mass of retina to the optic nerve, was about 1 mm. in diameter. It consisted of glial and connective tissue, with a few nerve fibers and small vessels. In its center was a large hemorrhagic cyst. The pyramidal mass of the retina lying behind the lens was fused laterally to the ciliary processes by areolar connective tissue and by masses of proliferating neuroepithelial cells. The middle of the posterior surface of the lens was adherent to a very thin layer of

hyaline tissue. No vascularization of this layer was seen. The main mass of retina showed empty and hemorrhagic cysts, hyalinized erythrocytes and occasional stratified layers of retinal cells. No folding or lobulation was evident. The vessels were small and few. A hemorrhage was spread over the posterior surface of the retina. The space between the pigment epithelium and the detached retina was filled with a hemorrhagic exudate. It contained fibrin and small masses of hyalinized red cells and clusters of epithelial cells.

The optic nerve was partly atrophic.

CASE 5.—A. S., a white girl, was born in an outside hospital July 14, 1939, after seven months' gestation, with a weight of 1,550 Gm. No instruments were used in the delivery. No trauma occurred. The cause of the premature birth was placenta previa. The infant was jaundiced, but not cyanotic, for a short time after birth. She was kept in an incubator in the hospital for two months after delivery. At the end of six months she weighed 6,250 Gm.

The mother was 26 and the father 30. The only previous pregnancy terminated in the delivery of a 6.5 month, premature infant, who died in two hours. The cause was placenta previa. The family history suggested no ocular or nervous diseases except for spinal bifida in a third cousin.

Immediately after the child was brought home from the hospital the mother noticed the white pupil in each eye. An ophthalmologist and the family physician, on examination of the eyes, suspected gliomas.

On Dec. 6, 1939 the child was given a medical, neurologic and ocular examination in the University Clinics. The condition was normal except for the eyes. The blood count and the urine were normal. Roentgenographic examination showed that the skull, chest and optic foramens were normal. The right eye showed a clear cornea. The left cornea gave a dull epithelial reflex. The anterior chambers were shallow. The irises were thin and slightly atrophic. The pupils were 3 mm. in diameter. With instillation of atropine, the pupils dilated irregularly, the right dilating horizontally to 5 mm. and the left to 5.5 mm. Just behind the lens in each eye a greenish white, homogeneous mass was seen. In the left eye a reddish brown area, noted later to be a hemorrhage, was seen off center temporally on the mass behind the lens. A diagnosis of bilateral retinoblastoma was made.

On December 8, before the operation, tension (Souter) was 12 mm. in the right eye and 36 mm. in the left eye. The left eye was enucleated. The right eye later showed intermittent glaucoma. Because of the pain, the right eye was enucleated on Jan. 30, 1940. At this time the circumference of the head was 42 cm. When the child was examined, on Aug. 3, 1943, she was healthy and active. There were no signs of mental retardation. On May 25, 1944 the artificial eyes were refitted. On Oct. 20, 1945 the condition of the child was unchanged, but she was erratic in her behavior.

Pathologic Examination.—Right Eye: The diameter of the bulb was 18.5 mm. anteroposteriorly and 19 mm. transversely. The bulb displaced 3.75 cc. of 4 per cent alcohol. The diameter of the cornea was 12 mm. The volume of the anterior chamber was decreased by the peripheral anterior synechias and by the adhesions of the pupillary half of the iris to Descemet's membrane. The chamber was filled with a light exudate. In most sections the root of the iris covered the filtration angle. The canal of Schlemm was collapsed. The sclera was normal. The pupillary portion of the iris was adherent to Descemet's membrane. The pupillary space was filled with a membrane of thin connective tissue, arising from the iris. The pigment epithelium of the posterior part of the iris formed small and moderate-sized cysts. The periphery of the iris was thin and was generally fused to the cornea. The central third of the iris was adherent to the anterior capsule of the

lens. The lens was normal. The pigment epithelium of the retina showed many proliferating clusters and layers of pigment cells. A heavy exudate filled the space between the pigment epithelium and the detached retina. It contained a multitude of red cells in various stages of disintegration and many ghost cells, particularly near the pigment epithelium.

The retina was detached from the disk to the ciliary body. It formed a stalk which joined the optic nerve. The main mass of the retina was consolidated into a flat pyramid, lying against the lens and the ciliary processes. The ora serrata was covered with a disorganized layer of pigment epithelial cells and strands of retinal, glial and connective tissue. The ciliary processes showed overgrowth of epithelial cells, frequently fused with connective and glial tissue. The space between the ciliary processes and the displaced iris was filled with a serofibrinous exudate and new connective tissue fibrils. A transverse sheet of amorphous, striated fibrous tissue was adherent to the posterior capsule of the lens. Laterally it became fibrillar and joined the overgrown epithelium of the ciliary processes. Posteriorly it was confluent with the retina. The retina was grossly plicated, atrophic and gliosed. A thin-walled intraretinal cyst, 1 mm. in diameter, was seen centrally behind the lens. Regular stratification was absent. A few lymphocytes, plasma cells and phagocytes were seen in the retina and in the choroid.

The optic nerve was slightly atrophic.

Left Eye: The diameter of the bulb was 20 mm. anteroposteriorly and 19.5 mm. transversely. The bulb displaced 4 cc. of water. The cornea was 11.5 mm. in diameter. The anterior chamber was absent centrally and was about 1.5 mm. deep laterally. The filtration angle was closed by the peripheral anterior synechias. The canal of Schlemm was collapsed. The sclera was slightly thinner than normal. The lens was normal. One-half the pupillary portion of the iris was adherent to the lens. At the pupillary border a few short filaments of connective tissue from the iris were adherent to the lens capsule. The iris and lens were in contact with the middle third of the posterior surface of the cornea, where the iris was adherent to Descemet's membrane. The choroidal, ciliary and iridic vessels were engorged. The ciliary processes were thin and atrophic and were surrounded with newly formed fibrin. The choroid and ciliary processes showed a few small areas of infiltration with lymphocytes, plasma cells, mononuclear cells and eosinophils. The pigment epithelial cells were irregular in size and occasionally in clumps. A few proliferating and disintegrating pigment epithelial cells were observed in portions of the retina, and many were noted in and around the region of the pars plana and the ciliary processes.

The retina was detached from the disk to the ora serrata. The main mass of the retina was behind the lens, where it lay against a thinly stratified, amorphous transverse membrane. Laterally the membrane was joined to the ciliary processes by thin filaments. The proliferating masses of glia and epithelial cells were fused to the ciliary processes and to the sides of the retina. Posterior to the lens two intraretinal cysts filled with red blood cells were present in the retina. A large cystic space, 12 mm. wide and 4 mm. deep, behind the main mass of the retina was filled with exudate. Its wall was composed of a thin layer of gliosed, unorganized retina. Its base was joined to the optic nerve by a stalk of gliosed nerve fibers. The gliosed atrophic retina behind the lens showed slight evidence of stratification. Only a few small circular nests of stratified cells around a cyst were seen. The space around the stalk was filled with exudate, containing, anteriorly, disintegrating red blood cells and, posteriorly, a dense mass of whole red blood cells.

The optic nerve contained more connective tissue than normal.

CASE 6.—J. K., a white girl, was born in another hospital on March 4, 1938, three and one-half weeks prematurely, with a weight of 2,840 Gm. The cause of the premature delivery was unknown. The labor under ether anesthesia was not prolonged. No instruments were used. The child was in good condition and was without injury. Postnatal revival was unnecessary. There was no jaundice after the first day of life. For the next three weeks she was kept in an incubator under an oxygen tent for recurrent cyanosis. On her discharge, at 3 weeks of age, her weight was 2,650 Gm.

The father, aged 32, and the sister, aged 17 months, were healthy. The mother, aged 26, had diabetes, and her sister has tuberculosis. No history of nervous or ocular disease in the family was obtained.

On March 29 the infant was brought to the University of Chicago Clinics for an examination. She was undernourished and underdeveloped. Complete blood counts and the urine were normal. Roentgenologic examination of the skull and chest showed no abnormalities. A diagnosis of malnutrition and retinoblastoma of the left eye was made by pediatricians.

A more complete ocular examination was made on April 15. The mother had observed no abnormalities of the eyes or of vision. The left upper lid drooped slightly but moved normally. The eyes tended to converge. The right eye seemed to be the useful one. The left bulb was slightly smaller than the right. The conjunctivas and corneas were clear. The pupils dilated to 5.5 mm. with atropine. In the right eye the anterior chamber was shallow. The iris was normal. The lens was clear. On the posterior surface of the lens a small remnant of the hyaloid artery was visible. The fundus was best seen with a —20 D. lens. The appearance of the fundus suggested incomplete albinism. The retinal vessels were visible posteriorly over the yellow fundus. The choroidal vessels were prominent over the equatorial region. The disk was chalk white and flat.

The anterior chamber of the left eye was shallow. The iris showed a few dilated radial blood vessels. The lens was clear. A greenish gray mass without noticeable blood vessels was best seen just back of the lens with a + 10 D. lens. A diagnosis of retinoblastoma of the left eye was made.

On April 14 the child had overcome recurrent cyanosis and began to recover lost weight. The circumference of the head was 36 cm. On April 24 the sagittal sutures were found to be separated. Hydrocephalus was developing as the child became less dehydrated.

On May 3 the left eye was removed. Six weeks later, when the child was last seen by an ophthalmologist, pronounced hydrocephalus was present. The circumference of the head was 42.2 cm. The fundus of the right eye was best seen with a —20 D. lens. The disk was white, and the fundus was albinotic from the lack of melanotic pigment. Nasally, the retina was grayish yellow as seen at the equator and greenish peripherally. No masses or plaques were seen. The child was discharged from the hospital on June 6.

On July 29 the child was having frequent recurrent attacks of choking and cyanosis. Her weight was 5,730 Gm.

The coroner's physician reported that on Aug. 21, 1938 the patient died, with extreme congenital hydrocephalus. No tumor was evident in the optic nerve or the cranium. The cerebral cortex was less than 1 cm. thick. The ventricles were widely dilated. The aqueduct between the third and fourth ventricles was blocked by fibrous adhesions.

Pathologic Examination.—Left Eye (fig. 4 *B*): The bulb measured 16.5 mm. anteroposteriorly and 17 mm. transversely. It displaced 3 cc. of 4 per cent alcohol. The cornea was 10 mm. in the vertical diameter and 11.5 mm. in the horizontal

diameter. Its appearance was normal. The canal of Schlemm was covered by the trabeculations of the slightly opened filtration angle and by the root of the iris. In many sections anterior displacement of the root of the iris and the ciliary body was seen. The anterior chamber was 1 mm. deep and was filled with exudate. The sclera was normal. The pigment epithelium of the pupillary border of the iris was adherent to the lens capsule. Projections of the iris stroma extended a short distance into the pupillary space and also around the pupillary border to the anterior surface of the capsule behind the iris. Small vessels passed from the surface of the iris over the pupillary space and also onto the capsule back of the iris. The lens and choroid were normal.

The retina was detached from the disk to the ora serrata. The shape of the retinal mass was like that of a lobulated funnel, with its stem attached to the optic nerve. The conical part was tapered to form a 90 degree angle and was composed of a thickened, irregular layer of retina. The apex of the cone was attached by a thin, short stem to a large, round mass of folded retina, which was closely joined to the optic nerve. The retina behind the lens was adherent to one side of the posterior capsule for 1.5 mm. and was also fused to a few ciliary processes on the same side. Some lobules of the retina were stratified. The bacillary layer formed tubular pseudorosettes. Large and small cystic spaces occurred in some lobules in all strata. The retinal cells of these layers were irregularly arranged and were frequently absent. A few large vessels were present in the stem of retina connecting the disk with the mass of retina.

The space between the retina and the lens contained a few fine fibrils of connective tissue and no blood vessels. Few or no remains of the vitreous were visible. The pigment epithelium was regular except for a few small masses of proliferating cells. The space between the detached retina and the pigment epithelium was filled with a pink-staining material, containing few red blood cells. Near the anterior retinal mass and the ciliary body the number of red blood cells was greatly increased.

The optic nerve was apparently normal. The lamina cribrosa was in place.

CASE 7.—G. D., a white boy, was born Oct. 14, 1937, with a questionable gestational age of 6.5 months. The weight at birth was 1,835 Gm. The circumstances concerning delivery are unknown. On the day of birth the infant, who appeared normal and in fair condition, was brought to the hospital and placed in an incubator. On the second day oxygen was used to combat the cyanosis. On two occasions, for one day, the infant was moderately jaundiced. After fifty days the child was discharged from the hospital, with a weight of 2,625 Gm.

The mother was 22 and the father 30 years of age. The pregnancy was the first. The mother had a cough and had lost considerable weight. The child's great-grandfather and great-aunt had had tuberculosis. There was no history of nervous or ocular disease in the family.

On May 10, 1938 the child was admitted to the University of Chicago Clinics for an ophthalmic examination. Three months previously the mother had noticed that the right eye was larger than the left eye and that the head was rapidly enlarging. The circumference of the head was 42.5 cm. Except for the eyes, the child appeared to be normal. The blood and urine were normal. The Wassermann reaction of the blood was negative. Roentgenographic examination of the skull and optic foramens showed no abnormalities. No mental retardation was evident.

Ophthalmic Examination (May 13).—The child had a tendency to hold his fist over the right eye, which was more prominent than his left eye. The left eye turned in 25 degrees. Only the right eye followed light and gave a pupillary reaction to light.

Right Eye: The fundus was best seen with a —20 D. lens after the pupil was dilated with atropine to 7 mm. The disk was pale. The central vessels were displaced temporally in an anomalous manner. The color of the fundus was that of a blond or partially albinotic person. No retinal mass was seen.

Left Eye: The cornea and lens were clear and the anterior chamber was deep. A greenish gray mass, over which a few retinal vessels passed, was seen behind the lens on the nasal side. A diagnosis of retinoblastoma of the left eye was made.

On May 24 the left eye was again examined. The iris and lens were now displaced forward, and the anterior chamber was collapsed. The tactile tension was normal. The disk was best seen with a —20 D. lens, but the finer picture of the disk and fundus was blurred. The visible background was albinotic. A dense opacity in the vitreous extended forward from the disk. In the periphery, particularly nasally, a greenish white mass was noted. An enucleation of the left eye for probable glioma was done.

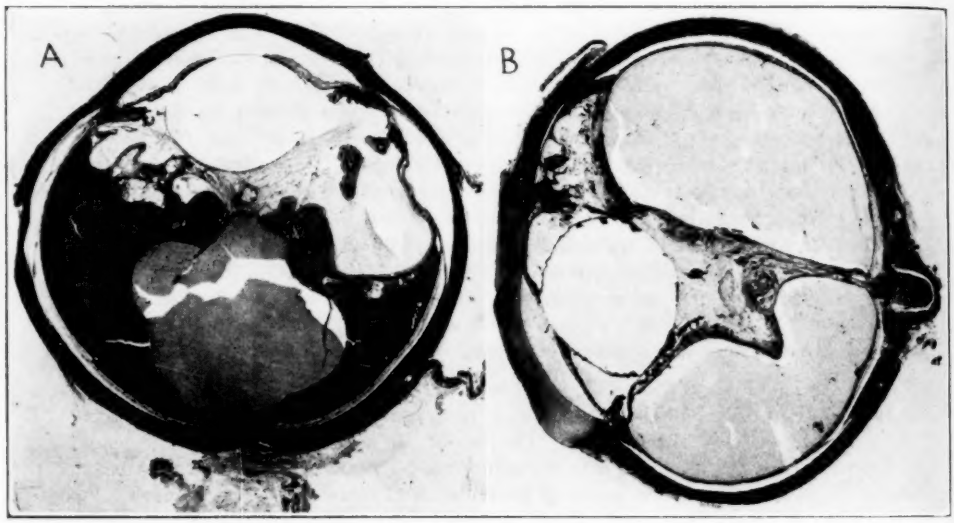

Fig. 5.—*A* (case 7), cross section of the left eye (× 4); *B* (case 8), cross section of the right eye (× 5).

Course.—On May 13, 1941 the right eye was reexamined. Vision was limited to large moving objects. A fine nystagmus was noticeable. The fungus was unchanged. The child was healthy and active mentally.

The child was still living in July 1944.

Pathologic Examination of Left Eye (fig. 5 *A*).—The bulb displaced 3 cc. of 12 per cent alcohol. It measured 17.5 mm. in the anteroposterior and 17.5 mm. in the transverse diameter. The cornea was 9 mm. in diameter. The anterior chamber was 1 mm. deep. The filtration angle and the canal of Schlemm were open. The sclera was normal. One third of the pupillary portion of the pigment layer of the iris was adherent to the lens. The lens was normal. No capsulopupillary membranes or vessels were seen. The choroid was normal. The pigment epithelium of the retina was roughened. On the inner surface of the retina a few phagocytes, proliferating epithelial cells, clumps of pigment cells and ghost cells were

present. The space between the pigment epithelium and the retina was filled with exudate, containing scattered red blood cells.

The greatly atrophic retina was detached from the optic nerve to the base of the first large ciliary process. The main mass of the retina was in the anterior third of the vitreous chamber. The mass laterally consisted of a thin layer of unorganized retina, the anterior lateral ends of which extended toward the back of the lens. The stalk was short, about 5 mm. long. On one side of the stalk, in the posterior third of the vitreous cavity, a cyst with a thin wall of retinal tissue, which was chiefly glial tissue, was fused to the posterior surface of the retina. It was filled with a noncellular exudate. The main retinal mass showed many large and a few small cysts filled with fibrin or fine connective tissue, a few tubular rosettes, slightly stratified retinal tissue and a few small blood vessels. Just behind the lens a thin layer of amorphous fibrous tissue lay transversely. The fine fibrils at the periphery of this layer extended to the posterior ciliary processes. The retina was fused posteriorly for about 2 mm. to the middle of the layer. A large space with a few filaments of connective tissue was present on each side posterior to the area of fusion. Only a rare capillary was seen in this area.

The optic nerve was apparently normal.

CASE 8.—B. K., a white infant, died twenty-four hours after delivery in another hospital. The mother, a 24 year old primipara, was unusually large at full term. Roentgenographic examination showed a large fetus with a large head. Cesarean section resulted in the birth of a hydrocephalic infant with bilateral talipes equinovarus. The suboccipitobregmatic measurement was 41 cm. and the occipitofrontal 47 cm.

The eyes were examined eighteen hours post partum. The microphthalmos was bilateral. The eyes showed extreme convergence. The pupils were of medium size and inactive to light. Oblique illumination of the pupils gave yellow reflexes. Intraocular tumors were suspected.

Autopsy revealed a thin, friable dura. A large amount of clear fluid escaped, and the brain substance collapsed to a small, shapeless, structureless mass. The cerebrum and cerebellum were not distinguishable.

The microphthalmic right eye was removed for study. The bulb had a volume of 2 cc. and measured 14 mm. in the anteroposterior and vertical diameters and 15 mm. in the horizontal diameter. No gross abnormalities were seen.

Histologic Examination of Right Eye (fig. 5 *B*).—The eye was 13 mm. in the anteroposterior and 15 mm. in the horizontal diameter. The bulb displaced 2 cc. of 1 per cent alcohol. The cornea was 7 mm. in diameter. The epithelial layer was three to four cells thick. The sclera was normal. The anterior chamber was 1.5 mm. deep and was filled with an amorphous exudate. The filtration angle was beginning to open. The canal of Schlemm was not seen in every section. The outer half of the temporal side of the iris was flush against, but not adherent to, the cornea. The pupillary pigment border of the iris was adherent to the lens capsule. A thin veil of iris stroma projected partly over the pupil. A few persistent capillaries from the iris passed over and around the lens to join the fine vessels behind the lens. The lenticular capsule was completely lined with a row of epithelium. The choroid showed relatively few vessels for the eye of an infant of this age. At points where the retina was attached the choroid formed thick, vascularized mounds. The pigment epithelium of the retina was mainly atrophic. The cells were small and scantily pigmented. Occasionally the pigment cells were formed in a double layer on the choroid and were scattered in the choroid and the detached retina.

Except for six mounds of thickened choroid behind the equator, where projections of the retinal tissue were attached, the retina was detached from the optic nerve to the first ciliary process. It was collected in a stalked, atrophic mass behind the lens and iris. The roots of the projections were divided by an incomplete layer of pigment epithelium. Breaks in the epithelium allowed a few small vessels to pass. The thick central stalk was composed of connective and glial tissue, with a few thin-walled, small arteries and veins. On the temporal side the pigment epithelium of the pars plana was detached. In part it formed a border for the mass of fine connective tissue anteriorly. All evidence of organized structure of the retina was absent. The space just behind the lens was filled with fine fibrils of connective tissue. Only a few small, thin-walled vessels were seen. No hyaloid artery was visible. The cavity behind the retina was filled with exudate. Massed red cells were in the spaces behind the iris, lateral to the lens and in front of the retina. Lymphocytes and round cells were around the retinal vessels and were scattered in the retina near the hemorrhages.

A few lymphocytes were seen in the choroid and the optic nerve.

The optic nerve was atrophic. The lamina cribrosa was not fully formed.

Fig. 6.—Drawing of the eye from the case of Becker and Raab,[7] showing multiple retinal synechias after retinal detachment.

Case 9.—N. E., a white girl, was born on Nov. 20, 1939, in the University of Chicago Clinics after forty weeks' gestation, of a 29 year old primipara. She was delivered with low forceps. The placenta was normal. The Wassermann reaction of the blood was negative. The weight at birth was 3,565 Gm. The infant was placed in an incubator and given oxygen for forty-eight hours to overcome the cyanosis. At birth a hematoma, about 5 cm. in diameter, was noticed over the left occipitoparietal region. The fontanels were tense and bulging. A diagnosis of cephalohematoma, subdural hematoma, subarachnoid hemorrhage, internal obstructive hydrocephalus, secondary glaucoma (left eye) and microphthalmos (right eye) was made. The right eye was small and the left eye large. The ocular movements were not conjugate and were irregular. Both eyes tended to turn downward on illumination.

On November 22 the right eye showed a clear cornea, 8.5 mm. wide. The anterior chamber was shallow. The radial vessels of the iris were prominent and

formed a persistent pupillary membrane. The iris appeared to be close to the cornea. The pupil was round, shaggy and fixed. Its diameter was 6 mm. The pupillary reflex was gray. A grayish, irregular membranous material appeared to lie deep in the fundus. A few fine, irregular red lines on its surface seemed to be blood vessels. At 5 o'clock a narrow strip of the fundus gave a red reflex. From 10 to 1 o'clock a wrinkled, yellow mass extended down 1 to 3 mm. from behind the iris on the edge of the pupil.

The cornea of the left eye was 12.5 mm. wide. The anterior chamber was not as shallow as that of the right eye. A persistent pupillary membrane was not so well developed as that of the right eye. The iris was normal. The pupillary margin was even and round. The pupil was 3.5 mm. in diameter and was fixed. The pupillary reflex was yellowish red. At 6 o'clock a small, irregular, fixed nodule was seen on or near the lens. The retina was poorly seen with a —20 D. lens. The disk was yellowish white and larger than normal. The retinal vessels were not distinctly seen. The corneas were cloudy when the child cried.

The diagnosis was microphthalmos, secondary congenital glaucoma, retinal tumor and blindness of the right eye, and secondary congenital glaucoma, retinal atrophy and blindness of the left eye.

On March 5, 1940 the eyes were found to be relatively unchanged. The pupillary membranes were atrophied. The tension (Souter) was 12 mm. in the right eye and 34 in the left eye.

In the following weeks repeated punctures of the fontanel gave a yellow fluid containing red blood cells. Examination of the blood and urine showed no abnormality. A series of roentgen treatments were given to the brain. The patient died suddenly on March 25, 1940.

An autopsy was performed by Dr. Paul E. Steiner. The diagnosis was of bilateral bronchopneumonia, aplasia of the cerebral cortex and cerebellum, agenesis of the corpus callosum and subarachnoid space, cerebral agyria, multiple heterotopias and congenital hydrocephalus.[5]

Histologic Examination.—Right Eye (fig. 7 *A*): The eye weighed 3.4 Gm. and measured 16.5 mm. anteroposteriorly and 16 mm. transversely. The cornea measured 8.5 mm. in diameter and was normal. The sclera appeared normal. The anterior chamber was 1.25 mm. deep. The trabeculae partly filled the filtration angle. The pupillary portion of the pigment epithelium of the iris showed minor foci of structural irregularity. Persistent remains of the embryonic vessels and mesodermal tissue of the iris passed from the iris to the anterior capsule of the lens, where it filled the pupillary space with a membrane, which was one to two cells thick. A few, fine vessels appeared on the anterior capsule. An overgrowth of the iris stroma attached to the iris projected upward behind the iris for 1.5 mm.

At points where the larger masses of membrane lay on the lens near the iris, the lens fibers were vacuolated. The posterior surface of the capsule was covered with the membrane, which had a central small pyramidal mass of cells with few capillaries. In the posterior pole of the lens the cortical fibers were disorganized, with debris, clefts and vacuoles. Several fine strands of cells pierced the capsule posteriorly and formed small nodules of proliferating cells just beneath the posterior capsule. The epithelium of the lens lined the capsule and occasionally formed more than one layer of cells. The ciliary body was small. The choroid was thin and relatively unpigmented. Only a few choroidal vessels were seen. The pigment epithelium of the retina was irregular in pigmentation and thickness. Occasionally the thin, gliosed retina was fused to the choroid. The melanotic pigment was scattered irregularly on the gliosed retina in small and large masses. The retina was about one-fourth the thickness of the normal retina. No normal cells or

stratification was present. The entire retina was a solid sheet of pigmented, gliosed tissue. Anteriorly, the retina continued as a detached retrolental membrane from a region in front of the ora serrata. It was fused to several ciliary processes. Behind the iris the membrane was composed of a mass of retinal tissue, which showed only a slight attempt at organization. The thinner portion of the membrane, behind the lens, touched the capsule and centrally was connected with a hyaloid artery, which was surrounded with a veil of mesodermal connective tissue. The hyaloid artery arose from a conical, heterogeneous mound of retinal and glial tissue on the disk. The optic disk was large and distorted, and one side was filled with unorganized retina, which showed multiple rosettes.

No evidence of vitreous fibrillae could be obtained with special stains.

A few lymphocytes, mononuclear and polymorphonuclear leukocytes were present in the uveal tract.

Histologic Examination.—Left Eye (fig. 7 *B*): The anteroposterior diameter was 24 mm. and the transverse diameter 24 mm. The weight was 8.1 Gm. The

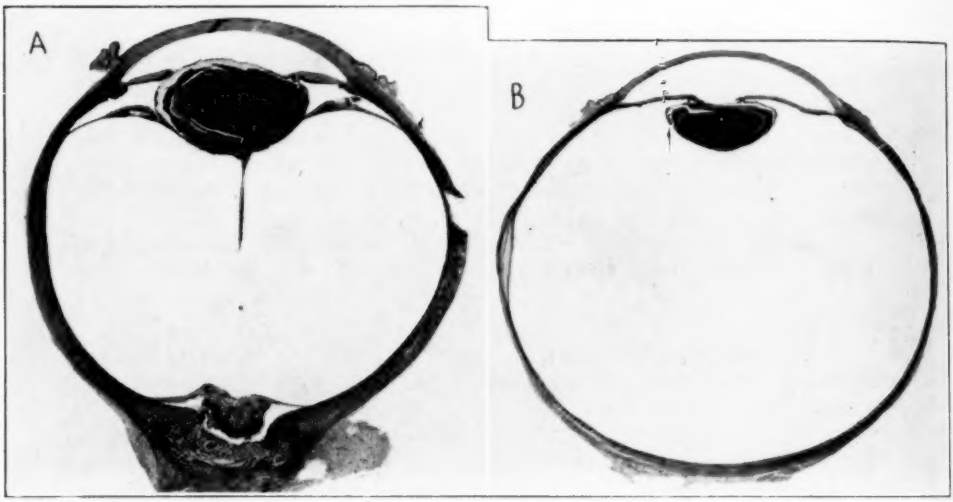

Fig. 7 (case 9).—*A*, coloboma of the optic nerve, transverse glial membrane, persistent remains of the hyaloid artery and cataract. *B*, gliosis of the retina; atrophy of the choroid, iris, ciliary body and sclera; secondary glaucoma, and cataract (× 4.5).

cornea was 12.5 mm. wide and was thinner and flatter than normal. The epithelium was about three cells thick in the middle. Few lymphocytes were present in the stroma. Occasional polymorphonuclear cells were on the posterior surface of the cornea. The canal of Schlemm was small and was absent in some sections. The anterior chamber was 2 mm. deep. The sclera was about one-half normal thickness. The iris and the ciliary body were atrophic. The thin, flat ciliary processes were far forward, one half on the ciliary portion and one half on the posterior surface of the iris. A few round cells and lymphocytes were present. The pupillary border of the iris was adherent to the lens capsule, and in places the pigmentation of the iris covered the pupillary area. The lens was flatter than usual. The posterior pole showed slight vacuolation. A small nodule of epithelial cells was beneath the posterior capsule.

The choroid was thin and its vascularity not prominent. A small segment of the retina extended forward to the root of the iris, where they formed a fold. The extensions were thicker and more stratified and organized than the rest of the retina. The retinal pigment epithelial cells were irregular in size. The pigment granules were scattered among the outer members of the bacillary layer. The nuclei of the outer nuclear layer of the retina were oval or long, and the cells

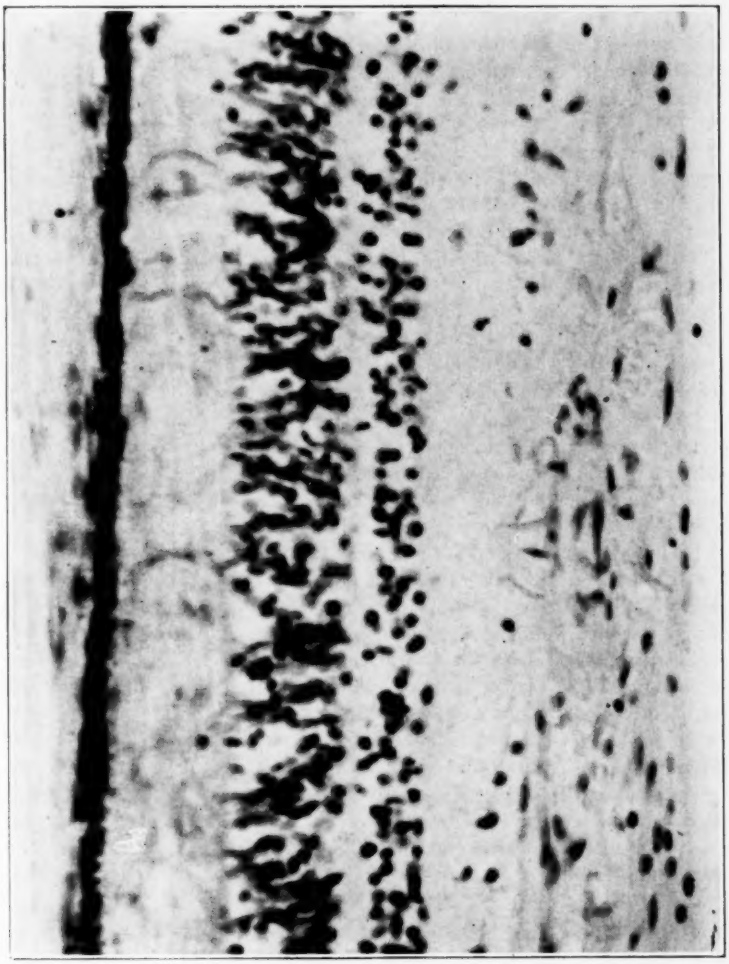

Fig. 8 (case 9).—Marked retinal atrophy and gliosis of the left eye.

showed filamentous processes. The outer limiting membrane was absent in the conspicuously unorganized outer nuclear layer. The outer reticular layer was slightly thinner than normal. The outer nuclear layer was thin, irregular and two to five cells deep (fig. 8). The inner reticular layer was thin or absent. The nerve fiber layer was heavily gliosed. Occasionally lymphocytes and mononuclear cells were seen on the surface of the retina. The surface of the papilla was gliosed. The

columns of nerve fibers in the optic nerve were irregular as a result of gliosis. A few leukocytes were noted.

CASE 10.—R. L., a white girl, was born in the University of Chicago Clinics in good condition without the aid of instruments on Aug. 4, 1938, at the full term of a second pregnancy. The placenta was normal. The weight at birth was 2,770 Gm. There was no evidence of hemorrhage, jaundice or cyanosis.

The father, aged 31; the mother, aged 30, and the sister, aged 3½ years, were healthy. There was no history of ocular or nervous disease in the family. There had been no previous abortions or miscarriages. The mother sprained her ankle in an automobile accident during her fifth month of pregnancy.

The infant was brought to the University Clinics for pediatric examination on Nov. 4, 1938. In October 1938 the infant had begun to have major convulsions several times a day. The convulsions were recurrent until Sept. 14, 1939, when the patient was last seen. The child was well developed physically, although obese, but mentally she was remarkably retarded. A macular, pigmented nevus, 4 cm. in diameter, was present on the right thigh. Neurologically, except for the eyes, a small head and the occurrence of convulsions, the patient was not abnormal. Roentgenographic examination of the skull suggested no cause for the convulsions.

The left upper eyelid was lower than the right. The pupils were equal in size. The right pupil reacted slowly, and the left was fixed. The external ocular movements suggested slight weakness of the left internal rectus muscle. A diagnosis of microcephaly and cerebral agenesis was made.

On Jan. 12, 1939 examination of the patient's eyes revealed a flat, gray mass in the right fundus, which had not been seen two months previously. The mother had observed nothing unusual about the eyes or vision. On January 13 the eyes were examined while the child was under ether anesthesia. The right palpebral fissure was slightly larger than the left. The external ocular movements were normal. The conjunctivas and corneas were clear. The irises were normal. The pupils were round and regular. The right pupil reacted slowly to light, and the left was fixed. The media were clear.

The right fundus was best seen with a —6 D. lens. Just above and below the pale disk along the superior and inferior nasal vessels were two gray-white plaques, about 2 disk diameters wide, which were sharply defined and slightly elevated. The retinal vessels passed over these lesions without change of direction. Five other small white, flat retinal lesions were on the temporal side next to the disk. The margins of the disk were blurred.

The left fundus was best seen with a —4 D. lens. The lesions measured about 1 disk diameter and lay close to the disk. A yellow-white plaque was just above and another was below the disk. The third spot was above and nasal to the margin of the disk. A tentative diagnosis of bilateral retinoblastoma was made.

On March 31, 1939 a reexamination of the fundi was made. The lesions were slightly larger and hazier in appearance than previously.

The right eye was removed on April 4, 1939. High voltage roentgen therapy was given to the whole skull and to the left eye. For a period of three months the lesions of the left fundus were constant in size, but later they became slightly larger. The blood cell count and urine were normal. The Wassermann and intradermal tuberculin tests gave negative reactions.

On Nov. 12, 1939, when the patient was admitted to a state institution, she had a chronologic age of 1 year 3 months and an intelligence quotient of 5. On Dec. 10, 1939 she had diphtheria, from which she recovered. On Jan. 31, 1940 she died of bronchopneumonia.

By permission of Dr. B. W. Lichtenstein, the neurohistologist, a brief report of the autopsy is given for comparison with that of Walker [5] :

"Postmortem examination revealed an advanced bronchopneumonic process, involving both lobes of the left lung and the base of the right; congestion of the liver; conspicuous congestion of some of the larger vessels of the brain, and gelatinous substance in the cerebellum.

"The brain weighed 576 Gm. without the dura. It was small, and the leptomeninges over the frontal lobes were thickened. The cortical gyri were irregular in size and shape. Some in the frontal lobes were large. Large and undular masses were present in some gyri in the frontal lobes. Other gyri were divided by tiny sulci, giving rise to microgyria. The parietal and occipital lobes were smaller than the frontal lobes. The arachnoid over the interpeduncular space was thickened. The first cranial nerves were absent. The optic nerves were small. A large cyst with a smooth wall was present in the right lobe of the cerebellum. The corpus callosum was absent except for two folds extending along the medial border of the lateral ventricles. There was no septum pellucidum. The walls of the lateral ventricles were studded with many irregular nodules. The third ventricle was greatly dilated. Heterotopic gray masses were disseminated throughout the cortex, internal capsule and caudate nucleus. The islands of Reil were irregular and cut by many shallow sulci. No mamillary bodies were seen in the section taken behind the tuber cinereum. The cornu ammonis was hardly recognizable. A large depression occurred in the right occipital lobe. A large heterotopic mass was seen in the right hemisphere of the cerebellum.

"Staining revealed massive and numerous heterotopias, composed of ganglionic cells, for the most part, which were small and were not well supplied with Nissl substance, and glia, which consisted of both astrocytes and oliodendrocytes. The cortex was normal except where the heterotopias disturbed the usual structure.

"The cerebellar cyst was a simple cavity without a distinctive lining.

"In the medulla the pyramidal tracts were small and the fibers scanty.

"The diagnosis was: (1) bronchopneumonia, with congestion and toxic changes in other viscera; (2) cerebral agenesis with heterotopias, involving (*a*) absence of the olfactory bulbs and nerves, (*b*) absence of the corpus callosum, (*c*) absence of the mamillary bodies and (*d*) microgyria, and (3) simple cyst of the right lobe of the cerebellum."

Histologic Examination.—Right Eye: The anteroposterior diameter of the eye was 19 mm. The cornea was 10 mm. in diameter. The anterior chamber was shallow. The canal of Schlemm was small and was not visible in every section. The pigment layer of the iris at the pupillary margin was adherent to the lens capsule. The choroid, ciliary body and lens were normal. The sclera was slightly thinner than normal.

The retina (fig. 9) corresponding to the several small areas of atrophy, as seen through the ophthalmoscope, showed unpigmented pigment epithelium. The cells of this layer were slightly larger than normal. The large lesions just above and below the disk were apparently formed by areas of lightly pigmented pigment epithelium. Nasal and temporal to the disk were two flat lesions, about 2 to 3 mm. in diameter. The temporal lesion showed multiple large microcysts in the inner and outer reticular layers and in the inner nuclear layer. Below the large fused microcysts of the retina the pigment epithelium was unpigmented. In the nasal lesion the cystic spaces opened into the subretinal fluid under an unattached retina. The subretinal cavity was evenly lined outwardly with unpigmented retinal epithelium. In the deepest part of the cyst, which was about 100 microns deep,

several pigmented and unpigmented epithelial cysts were seen in the subretinal fluid. The nasal side of the lesion showed a small fold of pigment epithelium overlying the subretinal cavity.

Temporally, an area 2.7 mm. in diameter, extending forward to within 1.5 mm. of the ora serrata, showed an irregular nerve fiber layer. Multiple short fibers extended from the nerve fiber layer into the vitreous. The greatest thickness of this layer was 1.6 mm. Near the ora serrata the bacillary layer of the retina

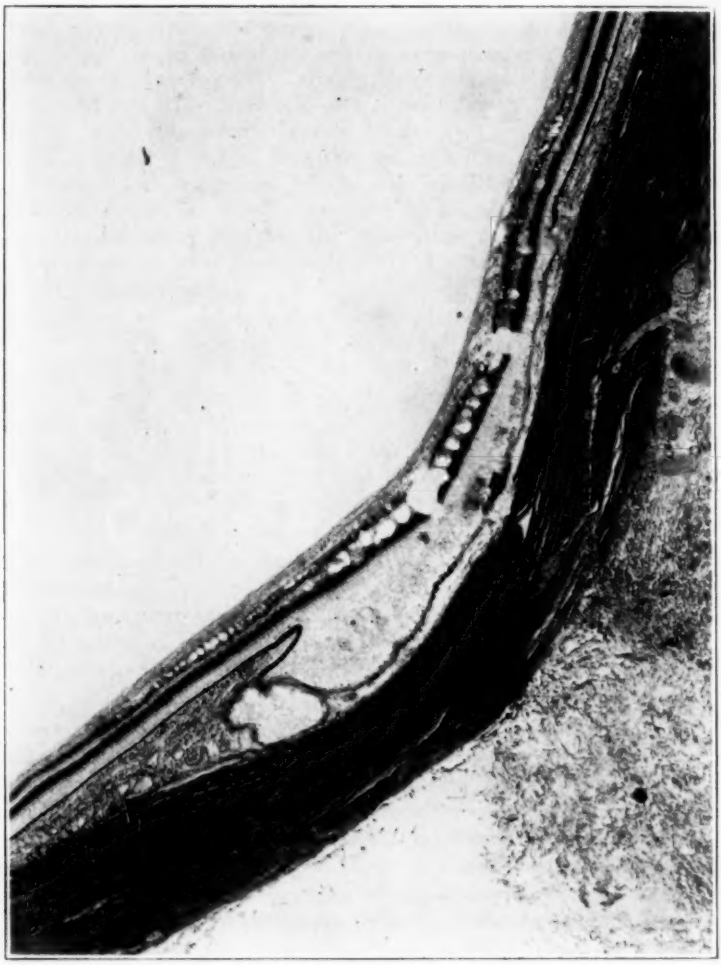

Fig. 9 (case 10).—Posterior part of the right eye near the disk.

was unevenly attached to the pigment epithelium and was distorted. A small narrow projection of unorganized retinal cells ran forward over the pigment epithelium as far as the ciliary processes.

The optic nerve was normal.

CASE 11.—J. Z., a white boy, was brought to the University of Chicago Clinics for an ophthalmic consultation on Jan. 20, 1944.

He was born in another hospital on Dec. 1, 1942, after seven months' gestation, with a weight of 1,360 Gm. No instruments were used in the delivery. The cause of prematurity was unknown. The child was placed in an incubator for twelve weeks. In the fifth month of pregnancy the mother had a bloody vaginal discharge for one day. During the sixth month she received intravenous injections of a "yellow fluid" three times a week, in spite of a negative reaction of the blood for syphilis. The mother believed that the father had a venereal infection, although his blood gave a negative serologic reaction. The father, aged 27 years; the mother, aged 27 years; two brothers, aged 4 and 5 years, a sister, aged 3 years, and other relatives were well and had no obvious ocular or nervous disease. No evidence was obtained by inquiry of the presence of virus diseases in the family during the first months of pregnancy.

When the child arrived home, at the age of 3 months, the mother noticed that the eyes behaved differently from those of other children and that they followed only bright lights. She was told by the obstetrician that the child was blind at birth. In another clinic, on May 21, 1943, a diagnosis of bilateral persistent tunica vesculosa lentis was made. As a result of examination, on June 6, bilateral retinoblastoma was suspected, and an operation was advised.

On Jan. 21, 1944 the child was examined in this clinic. A diagnosis of severe emaciation, hypochromic anemia and mental retardation was made. The child weighed 5,320 Gm. The circumference of the head was 41.5 cm. Roentgenologic examination of the skull showed no abnormalities. Agglutination tests with brucella, Pasteurella tularensis, and Proteus vulgaris OX19 gave negative results. The Kahn reaction of the blood was negative. The urine was normal. The red blood cell count was 3,800,000 and the hemoglobin was 3.8 Gm. per hundred cubic centimeters. The anemia was later cured by medication.

The head turned toward light, but the conjugate movements of the eyes were inconstant. Light perception was present, but there was no fixation. The corneas were 7 mm. in diameter. The pupils, 2 to 3 mm. in diameter, reacted slowly to light. The anterior chambers and irises appeared normal. The pupils did not give a red reflex. Gray, nonvascular masses lay behind each pupil, close to the lens. The retina of the right eye was given 700 r and the retina of the left eye 350 r.

On Feb. 17, 1944 another ophthalmic examination was made. Central visual fixation was not sustained. Externally the eyes were normal. The corneas were 7 mm. in diameter. The anterior chambers were shallow. The markings of the iris were blurred. The right pupil was 3 mm., and the left 2 mm. in diameter. With dilation with atropine the right pupil was 5 mm., and the left 3 mm., in diameter. Incomplete posterior synechias produced irregular pupils. A thin veil passed over the anterior surface of each lens. Posteriorly, close to each lens was an irregular, gray mass with peripheral vessels. The light reflex was a dull gray. Dentate processes were seen at the extreme periphery of the fundus of each eye. The tactile tension was normal. Dr. T. L. Terry, of Boston, made the diagnosis of retrolental fibroplasia.

On Aug. 8, 1944 the corneas measured 10 mm. in diameter. The left cornea was slightly hazy. The anterior chambers were almost collapsed. The right pupil measured 3 mm. and was round. The left pupil was ragged. Both pupils were bound by posterior synechias. The retina of the right eye was seen as a smooth gray mass, touching the lens. No retinal or iridic vessels were seen. The left eye showed an opaque lens. No vision or reaction to light was obtainable. Tactile tension seemed to be increased.

The child was malnourished, poorly developed and mentally retarded. On Nov. 27, 1944 the intelligence quotient on the Kuhlmann scale was 37.

A diagnosis of bilateral microphthalmos, congenital detached retina, anterior and posterior synechias and complicated cataract was made.

Case 12.—C. D., a white boy, was born July 23, 1941 in the University of Chicago Clinics after thirty weeks' gestation. The weight at birth was 1,745 Gm. Delivery was by cesarean section, after the mother had had a uterine hemorrhage. The placenta was normal. The cause of the prematurity was unknown. At birth respiration was delayed two minutes, and the cyanosis was moderate and transitory. There was no jaundice. The infant was kept in an incubator until August 22, when he was discharged from the hospital in a healthy condition with a weight of 2,505 Gm.

The father, aged 31; the mother, aged 28; a brother, aged 8 years, and three sisters, aged 6, 4 and 2 years, were well. The siblings were born after full term pregnancies and with normal deliveries. The second pregnancy terminated in six months with induced delivery after uterine hemorrhage. The premature infant, who was normal, died in seventeen minutes. The mother's sister had questionable tuberculous lymphadenitis, and the maternal grandmother was partly blind. No other member of the family had any ocular disease, and there was no history of nervous disease in the family. The mother's parents were cousins.

When the patient was 9 months old, he was treated for spasms by the family doctor, who noticed that the child was blind. The mother had been advised by two ophthalmologists that the child had pseudogliomas.

On Dec. 12, 1943 examination showed that the child was blind and mentally retarded. Gray masses, suggesting pseudogliomas, were seen back of each pupil. Examination of the blood showed mild anemia, and the spinal fluid was normal. The mother refused to permit further examinations.

On May 4, 1944 an ophthalmic examination was made. The child, according to his mother, was apparently blind in September 1941. The eyes did not follow light or blink on exposure to bright light. The eyes seemed small for the head. The right cornea was clear and measured 10.5 mm. in diameter. The anterior chamber was shallow. The pupil was 5 mm. in diameter and was bound down with posterior synechias. No pupillary membranes or vessels were seen. The posterior surface of the lens was completely covered with a gray, nonvascular mass except at the extreme periphery, where a red reflex was obtained. The left cornea was 10.5 mm. in diameter. The anterior chamber and iris appeared normal. The pupil reacted to light. No pupillary membranes or vessels were seen. A gray mass filled the upper half of the left fundus behind the lens. A grayish stalk, 2 mm. in diameter, containing blood vessels, extended back to a pale gray area of 1 papilla diameter, corresponding to the disk. Dark granular and clumped pigment was scattered throughout the rest of the fundus, which was reddish. No retinal vessels were visible. The choroidal vessels were fairly well seen.

A diagnosis was made of retrolental fibroplasia of both eyes and postinflammatory chorioretinitis of the left eye. Because of the blindness and cerebral agenesis with mental retardation, the child was committed to a state hospital in June 1944. He was still living on Aug. 11, 1944.

Case 13.—J. K., a white girl, was born Aug. 20, 1939 in an outside hospital after seven months' gestation. The weight at birth was 810 Gm. The second infant of the twins, born after J. K., died after five hours. For the first twenty-three days the child was treated with oxygen. She was kept in an incubator for one hundred days. Her weight was then 2,670 Gm.

The father, aged 37, and a sister, aged 6 years, had hereditary supernumerary toes. The mother, aged 36, showed persistent high blood pressure. Her mother at the age of 46 had a cerebral tumor. A sister of the infant's mother was obese. Sisters of the patient, aged 4 and 11 years, were normal. The family gave no evidence of mental retardation or signs of hereditary ocular diseases.

In May 1940 the mother observed that the right eye protruded. She was told by a physician that the child had cataracts. The blindness was noticed when the child was 3 months old.

On Jan. 13, 1941 the mother brought the child to the hospital for advice about blindness and lack of physical development. After an examination, a diagnosis of bilateral supernumerary toes, right hemiparesis and cerebral agenesis was made. The blood count and the urine were normal. The Wassermann reaction of the blood was negative. The supernumerary toes were removed surgically.

The child was photophobic. No sense of light projection was evident. The external ocular movements were normal. The left eye was enophthalmic. The eyes were equal in size. The right eye showed a central corneal nebula. The anterior chamber was shallow. The pupil, 3.5 mm. in diameter, was fixed by posterior synchechias. The lens was densely opaque. No fundus reflex was obtainable.

The left eye showed a clear cornea and lens. The anterior chamber was shallow. The pupil was 4 mm. in diameter, but it was not reactive to light. With homatropine the pupil dilated to 7 mm. The retina was green-gray and was detached as far as the ora serrata. It floated forward in the form of a funnel, obscuring the disk. The large retinal vessels ran posteriorly toward the hidden disk until they were hidden by the folds of the retina. No hemorrhage or tumor was noted.

On April 7, 1941, an attempt to extract the cataract of the right eye was unsuccessful because the lens was hard and opacity of the cornea interfered with observation of operation.

The patient was last seen Oct. 15, 1941. The condition of the eyes was unchanged.

Case 14.—J. S., a white girl, was born in the University of Chicago Clinics on June 2, 1937 after thirty-eight weeks' gestation. The placenta was normal. The weight at birth was 3,410 Gm. There was no postnatal cyanosis or jaundice. The child was normal except for the eyes, which were small and were kept closed. There was no sign of vision.

The mother, aged 18, a primipara, had had preeclamptic toxemia of pregnancy. The father, aged 25, was well. The parents knew of no familial disease.

The eyes were examined on June 15 in the University Clinics at the request of the obstetrician. The bulbs were smaller than normal and were deeply set in the orbits. The lids were kept partly closed. The eyes gave no reaction to light. They converged slightly, but the external ocular movements were unrestricted.

The right cornea was 6 mm., and the left 7 mm., in diameter. The anterior chambers were apparently of normal depth. The right cornea was slightly cloudy. Tactile tension could not be taken. The pupils were irregular and fixed to light. Behind the lens, a greenish gray mass was seen deep in the fundus of each eye. The mass was larger in the right eye than in the left. A diagnosis of bilateral glioma was made. Dr. Sanford Gifford, in consultation, examined the eyes on July 8 and expressed the belief that the child had microphakia, and not glioma.

On August 20 the corneas were seen to be clear, and the gray mass in each eye was close to the posterior surface of the lens. The child was repeatedly observed by pediatricians, neurologists and ophthalmologists.

Since the age of 1 month the head had steadily increased in size. On Aug. 30, 1937 the circumference of the head was 49 cm. A trephination showed that the cortex was thin and was lying close to the dura mater. A cloudy, yellow fluid was obtained from the ventricles. A diagnosis of hydrocephalus secondary to obstruction of the ventricular system was made.

Ophthalmic examination, on April 6, 1938, showed that the eyes were unchanged in size. The corneas were clear. The anterior chambers were not shallow. The lenses were cataractous. A diagnosis of bilateral pseudoglioma and cataract was made. On June 2, 1938 the head was 71 cm. in circumference, and the fontanels were wide and tense. Signs of meningeal irritation were present. There was no history of vomiting or convulsions.

The patient was last seen on Sept. 24, 1938. The condition of the eyes was unchanged. On Sept. 25, 1938 she was admitted to another hospital, where she died, March 5, 1939.

The diagnosis obtained from the autopsy record was congenital hydrocephalus, cerebral edema and pneumonia. No retinal glioma was observed.

Case 15.—D. H., a white girl, was born May 3, 1942 in the University of Chicago Clinics after a gestation of thirty-one weeks. The cause of the prematurity was unknown. After delivery respiration was delayed for two minutes. The weight at birth was 1,580 Gm. The child was placed in an incubator for twenty-six days and was discharged from the hospital at the age of 47 days. The weight then was 2,500 Gm. There was no history of cyanosis or jaundice.

The father, aged 40; the mother, aged 38; the brothers, aged 10 and 12 years, and the sisters, aged 16 and 20 years, were well. The family had no history of nervous or ocular diseases.

On August 8 the mother brought the child to the University Clinics for treatment of constipation. She had noticed no abnormalities of the eyes. Physical examination revealed for the first time a small, yellowish gray mass on the nasal side of the right fundus. A smaller gray mass was seen in the left fundus. The child was otherwise healthy. The weight was 4,200 Gm. Roentgenographic examination of the skull and optic foramens revealed nothing abnormal. The blood and urine were normal.

On Aug. 11, 1942 the eyes were examined again. Vision was nil. The anterior chamber of the right eye was obliterated. The iris pattern was blurred, but atrophy was not present. Anterior synechias were present. Posterior synechias were seen except at 3, 6, 9 and 12 o'clock where the pupillary reflex was dark. The pupil measured 3 mm. in diameter and was fixed and elliptic. A yellowish gray mass behind the lens filled the middle of the pupillary space. It was traversed by small vessels arising from the superior nasal and temporal quadrants. The mass was high in the center and was distinctly seen, but peripherally it appeared blurred.

The changes of the left eye were similar to those of the right eye. The anterior chamber was obliterated. Complete anterior and posterior synechias were present. The iris was not atrophic. The pupil was round and fixed. A yellowish gray mass filled the space behind the lens and gave a gray pupillary reflex. The mass showed a wavy surface, which was darkened in spots with pigment. Small retinal vessels from the four quarters of the fundus passed over the mass. The central mass in each eye was best seen with a +20 D. lens. A diagnosis of probable bilateral detachment of the retina was made.

In another clinic, on April 23, 1943, the eyes were found to show little change. The infant was mentally retarded.

CASE 16.—R. F., a white boy, was brought to the University of Chicago Clinics on April 10, 1941 by the mother, who said that the child had never been able to sit up, to hold his head up, to walk or to talk. He was born in another hospital on Feb. 4, 1938 after seven months' gestation. The cause of the prematurity was unknown. The weight at birth was 1,770 Gm. The infant was kept in an oxygen tent for three weeks and was discharged from the hospital after five months. The child had always been blind. His eyes were never fixed on his parents or on moving objects. Objects were not grasped unless they were placed in his hands. He had never had convulsions and had never been injured.

The father, aged 30; the mother, aged 26; the brothers, aged 4 and 6 years, and a sister, aged 1 year, were well. The parents knew of no nervous or ocular disease in the relatives or ancestors.

Physical Examination.—The child was small and weak. The weight was 10.2 Kg. The urine was normal. The red blood cell count was 5,150,000, and the hemoglobin content was 8 Gm. per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative. Roentgenographic examination showed a normal skull. Vision was nil. The bulbs and corneas were normal in size. The anterior chambers, irises and lenses appeared to be normal. The pupils gave no reaction to light. With atropine they dilated to 4.5 mm. In the right eye a gray mass of detached retina, traversed by retinal blood vessels, was seen to extend from the temporal side of the disk to the periphery. The mass was best seen with a +7 D. lens. On the nasal border of the mass a yellow-gray area, 1 disk diameter in width, ran vertically over the disk. The nasal half of the fundus was pale, flat and indistinct. It was best seen with a +2 D. lens. The left fundus was similar to the right. A central gray mass, which was best seen with a + 8 D. lens, covered the disk and the macula. It arose from the retina in sharp vertical ridges. The retina laterally and superiorly was pale, indistinct and slightly elevated. The tension (Schiøtz) was 19 mm. of mercury in the right eye and 21 mm. in the left eye.

A diagnosis of spastic quadriplegia, cerebral agenesis and bilateral congenital detachment of the retina was made.

CASE 17.—B. B., the first of identical white female triplets, was born without difficulty on Jan. 30, 1943 in the University of Chicago Clinics after twenty-nine weeks' gestation.

The second triplet was normal at birth but died at the age of 4 months of pneumonia. The third triplet was previable and died thirty hours after birth. Postmortem examination of the third triplet was performed by Dr. Edith Potter. The child weighed 920 Gm. and was 37 cm. long. The pathologic diagnosis was: viability; constriction rings on the proximal phalanx of the first and fifth toes; fusion of the third and fourth toes of the left foot, and amputation of the first four digits of the right foot from amniotic bands; atelectasis, and collapse of the alveoli. The brain and other organs were normal.

The single placenta, weighing 756 Gm., had three cords attached marginally at equal distances. There were three amniotic sacs and a single chorion.

The father, aged 28; the mother, aged 27; a sister, aged 3 years, and the grandparents and great-grandparents were well. There was no history of nervous or ocular disease in the family or ancestors. The mother had measles when she was a child. The Wassermann reaction of the mother's blood was negative.

The patient weighed 1,085 Gm. on the fourteenth day of life. She was kept in an incubator and was discharged from the hospital in sixty-four days. For the first ten days in the hospital she was jaundiced. At the age of 105 days she had pertussis for six weeks. In April roentgen therapy was given to a cavernous hemangioma, 3 cm. in diameter, on the chest.

On June 15, 1943 the patient was taken to the University Clinics for a routine examination. The mother had noticed no defects in the eyes or vision of the infant. Examination showed a premature child in good health, with a weight of 5,220 Gm. The child was normal except for a white mass behind the lens on the nasal side of the fundus of the left eye. A diagnosis of pseudoglioma of the left eye was made by a pediatrician.

On July 8 it was noted that the eyes followed light but not objects. Occasionally the eyes showed a tendency to convergent squint. The corneas and irises were normal. The pupils were reactive to light. The nonvascular, white opacities seemed to be in or next to the lens. The fundus reflex was red. The skull and optic foramens appeared normal in roentgenograms.

Reexamination of the eyes on Sept. 14, 1944 showed searching movements and occasionally a convergent squint. The right eye followed blocks 1 inch (2.5 cm.) square, held close to the eyes. Vision of the left eye was apparently limited to light perception only. The corneas were 10 mm. in diameter. The anterior chambers were shallow. The irises seemed normal. The right pupil was more reactive to light than the left; the pupil dilated to 8 mm. with atropine. The right lens was clear. The left lens was clear except for a few irregular, translucent radial striae. Just behind the right lens, from 3 to 5 o'clock and 5 mm. from the center, was a nonvascular, smooth-surfaced, gray mass. Peripherally, behind the iris, the multiple radial, black and white ciliary processes joined the mass, which extended laterally and backward as a broad-based stalk, fused to the nasal side of the fundus and to the invisible optic disk. No vessels were seen on the stalk or the retina. Several crescents of dark granular pigment were around the site of fusion of gray tissue to the posterior pole of the fundus. The fundus was best seen with a —25 D. lens as a diffuse red reflex without vascularity.

The mass behind the left lens was seen nasally 2 mm. from the center. It covered the posterior surface of the lens from 7 to 12 o'clock and extended nasally as a winged, broad-based stalk to the area of the disk. Few floating pigment granules were observed in the postlental space. No vessels were seen. The nonvascular, red surface of the fundus was best seen at —25 D. The intraocular tension (Souter) was 10 mm. in the right eye and 16 mm. in the left eye.

Psychometric tests indicated that the child was retarded mentally by blindness and by the excessive protection and care of the mother.

A diagnosis of bilateral congenital retinal fold was made.

Case 18.—B. W., a white boy, was born in Chicago Lying-In Hospital on Jan. 12, 1944 after thirty weeks' gestation. The weight of the infant was 1,150 Gm. and the length was 36 cm. Because of the loss of amniotic fluid twelve days previously, abruptio placentae was suspected, and birth was induced with artificial rupture of the membranes. No instruments were used in the delivery. The newborn infant showed no signs of cyanosis, jaundice or hemorrhage. The Kahn reaction of the mother's blood was negative. The father, aged 23; and the mother, aged 17, were well. The child was the result of a first pregnancy. There was no history of ocular or nervous disease in the family or the ancestors.

The infant was given vitamin K and placed in a Hess bed with a constant supply of oxygen. The child was healthy during his stay in the hospital except for persistent nonpitting edema of the legs. On discharge, at the age of 65 days,

he weighed 2,540 Gm.; the hemoglobin content was 10 Gm. per hundred cubic centimeters, and the red blood cell count was 3,100,000. The eyes appeared normal.

The condition of the infant's health was followed at a welfare station. On Sept. 26, 1944, by request, the child came to the University Clinics for examination. He was not gaining weight well. The mother observed that the infant had not been able to fix his eyes on objects for the past three months. Examination showed a small child, weighing 6,100 Gm., who was underdeveloped physically. His length was 62 cm., and the circumference of his head measured 41 cm. He was unable to sit up alone but was able to roll to one side. His blood picture was that of hypochromic anemia. Roentgenographic examination revealed a marked retardation of bone development in the extremities. A psychometric test indicated pronounced mental retardation not related to poor vision or prematurity. The pediatrician noticed a retrolental mass bilaterally. A diagnosis of immaturity, nutritional anemia, cerebral spastic palsy, bilateral retrolental fibroplasia and mental retardation was made.

On September 27 the eyes were examined. There was no response to light. Externally the eyes were normal. The corneas were clear and measured 10 mm. in diameter. The anterior chambers were shallow. Anterior and posterior synechias were present. The pupils, 3 mm. in diameter, were irregular and fixed. Atropine and neo-synephrine produced slight dilatation. The lenses were clear. In the right eye behind the lens was a pink-gray mass, which was wrinkled like parchment. Radial vessels of the same caliber as normal retinal vessels were seen in the center of the mass. No details were noticed in the peripheral indistinct orange reflex. In the left eye a pink-gray avascular mass was seen just behind the lens. Nasally and peripherally a blurred, indistinct orange reflex was obtained.

A diagnosis of bilateral congenital detachment of the retina was made.

The patient was last seen on Oct. 25, 1944. The physical condition was unchanged.

PATHOLOGIC FEATURES

A total of 16 eyes were removed surgically, because of blindness with intolerable pain or a presumptive diagnosis of retinoblastoma, or at autopsy. The eyes were fixed in Held's solution, embedded by means of the slow pyroxylin method and sectioned serially. Various appropriate staining methods were employed to show histologic structures and processes.

Microphthalmos.—The presence of microphthalmos in the first few months of life of a premature infant is difficult to determine. An eye may be abnormally small at birth because of prematurity, congenital microphthalmos or arrested growth due to detached retina or other pathologic process. Furthermore, a microphthalmic eye may have a secondary glaucoma, which increases the size of the eye but not its structural parts.

Of the 9 microphthalmic eyes, 7 had a totally detached retina, which in most instances was relatively well atrophied. The clinical secondary glaucoma in 3 of these eyes was either of too short duration or too transitory to effect the size of the eye. The full term infant with microphthalmos had a long-standing retinal detachment and retinal synechias at birth, with no signs that intrauterine glaucoma had affected the size.

The detachment of the retina may hinder the growth of the bulb, but the evidence was not remarkable in these infants with a gestational age of 7 months or less. Two of the 9 microphthalmic eyes had no retinal detachment. One showed general retinal dysplasia, and the other, general retinal gliosis, atrophy and glial hyperplasia of the anterior part of the retina and persistent hyaloid artery. A large eye with gliosis of the retina, which was not included with the 9 microphthalmic eyes, was microphthalmic in structure but became large probably as the result of secondary early fetal glaucoma of long duration.

Cornea.—The diameter of the cornea varied with the gestational and the living age and with the amount of intraocular pressure. The diameter of the microphthalmic eyes was generally within the lower limit for the normal eye of the corresponding total (i. e., living and gestational) anatomic age.

Glaucoma after a retinal detachment of long duration, which was indicated by almost complete atrophy of the retina, produced a bulb of average size or slightly larger, a thin sclera and choroid and a large cornea in an eye with partly arrested growth. Congenital glaucoma in an eye with complete retinal gliosis resulted in a greatly enlarged bulb with a thin sclera and a thin cornea of abnormally large diameter. It seemed that a glaucoma lasting several months enlarged the bulb, stretched the sclera and widened and thinned the cornea during the late prenatal or early neonatal period.

Anterior Chamber.—The anterior chamber was of normal depth in the eyes with the iris beginning to adhere to the lenticular capsule. After complete posterior synechias formed and a heavy exudate occurred in the intraretinal space, the anterior chamber became shallow. The chamber was almost totally collapsed after exudate and hemorrhage entered the space posterior to the iris. In some eyes the iris and the lens were pushed forward into the space of the anterior chamber. In most of the eyes the filtration angle was immaturely developed and the canal of Schlemm was partly covered. The effect of age, prematurity and arrested growth on the immaturity of development of the trabeculae and the filtration angle is difficult to determine. In some eyes the filtration angle was closed in various degrees by the adherence of the periphery of the iris to the cornea as a secondary effect. In 1 eye central anterior synechias were present. The anterior synechias were a part of the process that followed the detachment of the retina.

Iris.—In eyes without retinal detachment there was a tendency for the iris to agglutinate, and later to adhere, to the lenticular capsule. In the eyes with pronounced inactive gliosis of the retina the posterior synechias probably indicated only part of a disease process of long duration before birth. Apparently, after the retinal detachment the

iris became engorged and then edematous. Later, cysts of iridic pigment epithelium formed in some eyes. Proliferation and extension of new strands of connective tissue and fine capillaries from the adjacent anterior layer of the iris onto the lenticular capsule occurred in several eyes. Since early clinical examination of the pupillary area revealed no traces of these vessels or connective tissue strands, they were not vestigial remains of a fetal vascular system. In 2 eyes the new strands passed through the pupillary area toward the equator of the lens and terminated there. In an eye with a collapsed anterior chamber and with central and peripheral anterior synechias, proliferation of connective tissue, pigmented cells and capillaries occurred in the pupillary space.

Ciliary Body.—The ciliary body and iris became atrophic during the persistent glaucoma. In the eyes with fetal glaucoma the ciliary processes were atrophic, but in the eyes with glaucoma occurring after retinal detachment the cellular reaction varied seemingly with the degree of intraocular pressure and the amount of intraretinal and postiridic exudate and hemorrhage. A low intraocular pressure and the presence of exudate with much protein tended to produce more proliferative response from the ciliary epithelium, neuroglia and connective tissue cells. As a result, a lamellar hyaline and connective tissue membrane formed to a greater or less degree behind the lens and extended transversely over the anterior limits of the detached retina.

Sclera.—The sclera was stretched thin in eyes with long-standing glaucoma. The lamina cribrosa was only slightly deflected outwardly, if at all.

Choroid.—The choroid was immature in development in the younger premature infants. Frequently the choroid was engorged after retinal detachment if the cellular reaction of the anterior uveal tract was intense. Very heavy exudation in the intraretinal space was usually accompanied with separation of the anterior epichoroidal lamellas by a serofibrinous exudate.

Prolonged glaucoma produced atrophy of the choroid. In the eyes with the gliosed retina the atrophic choroid was fused to the retina. In the one eye of the full term, 1 day old infant born with a bilateral detached retina the retina was reattached in six places. The retinal synechias were identical in appearance with those shown by Becker and Raab [7] in the picture of primary retinal detachment (fig. 7). The choroid was hypertrophied and well vascularized at the junction with the retinal synechias. That this process occurred in fetal life is obvious, as the

7. Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1916, pt. 2, chap. 10a, no. 2, pp. 1453 and 1560.

infant died during the first day of life. In the eyes with dysplastic retinas the choroid was relatively hypoplastic.

Retina.—The retina was the tissue commonly affected in eyes with congenital encephalo-ophthalmic dysplasia. The retina in the sections of 2 eyes was dysplastic. The nerve elements were hypoplastic, and the supporting nerve tissue was hyperplastic. An abnormal, unorganized overgrowth of retina at the ora serrata, agenesis of melanotic pigment in the pigment epithelium of the retina, glial hyperplasia of the retina, hypoplasia of the nuclear layers and a coloboma of the pigment epithelial layer of the retina occurred. In both eyes one or more small serous separations of the retina between the pigment epithelium and the bacillary layer were evident. There is a good possibility that the retinal detachment began locally with a choroidal effusion. It could explain the small pigmented lesion after retinal atrophy which Terry described in the eye of 1 of his patients, as well as the lesions in these 2 eyes.

In 2 eyes the anterior part of the retina was overgrown and formed a transverse postlental membrane after atrophy and gliosis.

Complete detachment of the retina was found in 12 eyes. The retina was usually massed forward behind the lens and the iris. If detachment happened early before birth, the stalklike base was a glial shaft of nerve fibers extending to the atrophic retina. No definite, large hyaloid artery could be seen. In a few eyes part of the retina was a fused mass at one side. The remainder of the retina was detached, like a sac, which was displaced anteriorly. The retinal mass in some instances was extremely atrophic. The nerve cells were almost entirely absorbed, and only large glial and small connective tissue strands remained. This late atrophy of the retina explained the increasing redness of the pupillary reflex as the disease progressed in some eyes.

It is possible that the retinal atrophy followed the flat detachment produced by the serous effusion in the first 2 eyes; if this is true, the process of gliosis of the retina in the other 2 eyes would be similarly explained.

Optic Nerve.—The optic nerve in the eyes of the infants over 2 months of age was almost completely medullated. The optic nerves in the eyes with a totally gliosed retina could not be examined properly. In the eyes with fetal detachment of the retina, with pronounced retinal hypoplasia and with detachment of long duration, the number of nerve fibers seemed to be less than normal. In 2 eyes the nerve head showed malformations.

Lens.—The lenses in eyes with a detached retina showed no abnormalties except for proliferation of the lens epithelium beyond the equator after long detachments. The total cataracts with pronounced changes

were found in the eyes with complete retinal gliosis. In the microphthalmic eye with the hyaloid artery and gliosis, proliferating capillary endothelium broke through the posterior part of the capsule.

General Pathologic Features.—Congenital encephalo-ophthalmic dysplasia seems to affect the neuroectoderm primarily and the associated structures secondarily at an early fetal age. Development of the cerebral cortex may be retarded as early as the fetal age of 10 weeks. The basal ganglions and the brain stem are not evidently involved in the disease. Cerebral hyperplasia, hypoplasia and heterotopias are found. Hydrocephalus, if it occurs, is perhaps related to an anomalous development of the arachnoid membrane.

The development of the eye may be affected in early fetal life in the same manner. In the cases of severely affected development the manifestations are microphthalmos, malformation of the optic nerve head, and hyperplasia and hypoplasia of the retina. The intraretinal serous effusion and retinal detachment may follow later. The retina degenerates and atrophies. Posterior synechias form. Proliferation of the glia, mesodermal connective tissue and neuroepithelium may lead to the formation of a transverse retrolental membrane and of iridic and postlental capillaries. Intraocular exudation and hemorrhage, anterior synechias and cataracts are other complications. Secondary glaucoma is common. Leukocytic reaction is slight.

ETIOLOGIC FACTORS

The records of the 18 cases presented here served as the basis for a study of the origin of the disease. The recorded details permitted the grouping of factors that had a bearing on the causation.

Hereditary and Familial Tendencies.—There was no evidence based on the statements of the parents that the disease was inherited directly from relatives in the mother's or the father's immediate family or in the ancestors. Furthermore, there was no second occurrence of the disease in the family in other, later pregnancies. Of course the value of family history was limited by the small number in the family, by the lack of knowledge concerning the relatives and by the great mobility of people under present social conditions. The only prominent hereditary factor not related to the disease was the presence of supernumerary toes in 1 child. This inheritance was traced to the father and the paternal ancestors.

The disease and prematurity were unrelated to the environment of the infant. The families were not in any one social stratum. The occupations of the fathers ranged from relief projects, employing the poverty-stricken, incompetent unemployed to the independent professions. Social conditions apparently were not related to the disease or to prematurity.

Age of Father and Mother.—The range of ages of the fathers and mothers was similar to that of fathers and mothers of children without this ocular disease. There is no relation of the incidence of this disease to the age of the mother, like that which occurs with mongolism, or to later pregnancies, like that which is associated with the Rh factor. The distribution of the ages of the mothers at the time of birth was as follows: Three were from 15 to 20 years old; 4, from 21 to 25; 7, from 26 to 30; 1, between 31 and 35; 2, from 36 to 40 years, and 1, between 41 and 45. The distribution of the ages of the fathers at the time of birth was as follows: Three were from 20 to 25 years old; 6, from 26 to 30; 3, from 31 to 35; 2, from 36 to 40; 1 between 41 and 45, and 3 were of unknown ages.

Time of Conception and Birth.—It was believed that the ocular and cerebral disease and prematurity might be related to an unknown infectious disease of the mother which might be more prevalent in certain months and seasons of the year. It was hoped that a study of the distribution of the times of birth and of the times of similar developmental stages of the fetus would give a clue to such a disease. When the month of conception was calculated from the gestational age, the distribution of the times of conception was remarkably evenly spaced throughout the year. The number of conceptions varied from 1 to 2 per month, and only once was it 3 per month. The distribution of births according to month of birth was regular, ranging from 1 to 2 per month except for one month, with 3 births. There was no predominance of births in a series of months or in any one season. But if the distribution of births is arranged according to months of the year, it appears that the 3 births in 1937 were between October 14 and December 22; in 1938, 4 were between February 4 and August 4; in 1939, 4 were between July 10 and November 20, and the others were scattered from 1941 to 1944. The calculation for the time of conception shows a definite nonseasonal grouping, which may be significant. The 3 infants born in 1937 were conceived between March and June; the 4 born in 1938 were conceived between July and November; the 4 born in 1939 were conceived in January and February; the 2 born in 1942, in July and October; the 2 born in 1943, in July, and the other 2, in 1943 and 1944. The records of the municipal and state health reports for this part of the country have given no suggestion of an increase in any disease which may be related to these periods.

Number of Pregnancies.—Some diseases of infants and pregnancy are related to the number of pregnancies. Syphilis is a classic example of such a disease, the severity decreasing with the number of pregnancies. In the present cases, the infant was the result of the first pregnancy of 7 mothers, of the second pregnancy of 5 mothers, of the third pregnancy of 3 mothers, of the fourth pregnancy of 2 mothers

and of the fifth pregnancy of 1 mother. The distribution was in the range of the normal number of pregnancies. Infants born of further pregnancies were not affected with the disease. Each of the 18 infants was the only child in his family who had this ocular defect and the associated nervous disease.

Multiple Births.—Multiple births were found by Hess and associates [8] to be the most common single cause of premature labor. In 4 of Terry's cases and in 1 of Wehrli's [6] series, the infants were twins. In my 18 cases, there were 2 sets of twins and 1 set of triplets, all of whom were born between the twenty-ninth and the thirty-second week of pregnancy. Only 1 infant survived in each set; the others died shortly after birth except for one of the triplets, who died at the age of 4 months. Autopsy on 1 of these infants who died at birth showed nothing significant except for previability. Although the number of multiple births in this series of cases was high in proportion to the single births, it was not suggestive of any definite positive connection with the disease except for prematurity. There was no definite evidence for or against the presence of the disease in the other infant or infants of the multiple births except for the absence of any abnormality but previability in 1 child. It was possible, but not probable, that the disease was not sufficiently developed to be observed clinically or to be detected in pathologic examination in the other child or children of the multiple birth. The predominance of the neurodysplasia in infants from multiple pregnancies cannot be disregarded and may be a clue to the origin of the disease.

Sex of Child.—Sex apparently was not involved in the incidence of the disease. It was slightly more frequent in females than in males. Seven of the infants were males and 10 were females.

Race.—All infants were born of white parents, and no nationality was predominant. In Providence Hospital for Negro patients no cases of the disease have been seen by the ophthalmologists.

Frequency.—The incidence of the disease was about 1 per 16,000 new patients attending the University of Chicago Clinics. When the estimate was based on new patients from the time when the disease was first diagnosed to the time of writing, the ratio was 1 : 8,000 new patients. The ratio of cases in Chicago Lying-In Hospital to the number of total births was 1 : 4,000. All the patients were born in Chicago or its suburbs except 1, who lived in a small city near Chicago.

Weight at Birth.—Some obstetricians place infants weighing less than 1,000 Gm. at birth in the class of previable infants, which have an extremely high mortality rate, of about 99 per hundred. The prema-

8. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934.

ture infants with a weight at birth of from 1,000 to 1,500 Gm. have a death rate of about 25 per hundred. The premature infants weighing from 1,500 to 2,500 Gm. have a good survival rate. If weight is used as the basis of judgment, then 13 infants were premature and 4 were mature. Four infants at birth weighed from 800 to 1,000 Gm.; 4, from 1,000 to 1,500 Gm.; 5, from 1,500 to 2,000 Gm.; 2, from 2,500 to 3,000 Gm.; 1, from 3,000 to 3,500 Gm., and 1, from 3,500 to 5,000 Gm. There was no doubt that the disease is commonly associated with small premature infants. The ratio in these cases is 13:4 in favor of prematurity. However, this disease is also associated with infants with a normal average weight at birth.

Gestational Age.—The gestational age has always been difficult to estimate in weeks. It is usually based on the menstrual history. Only in unusual circumstances has it been determined exactly. For example, when soldiers have been home on a short leave of absence, the wives may know the date of conception. Generally the woman has a doubtful idea of the time interval. For this reason some obstetricians believe the gestational age may be missed by several weeks or by a month. Although most of the mothers were followed in the prenatal clinic, the weeks of pregnancy in these cases may vary in the same manner. When the weight of the child at birth does not accord with the gestational age, the menstrual history may be deceitfully or incorrectly given or may be naturally undeterminable.

Infants born with a gestational age of under 28 weeks are generally regarded as previable. Those who have a gestational age of less than 32 weeks have a mortality rate of about 25 per cent. Premature infants with a gestational age of between 32 and 38 weeks have a low death rate. It is believed by obstetricians that more premature infants, particularly in the early premature group, survive now and that many of the children with this disease fall in that group. However, some premature children have survived in the past, but the disease has not appeared to be associated with prematurity. In the report of Hess [8] on 200 cases of prematurity this disease was not seen in spite of careful observation and repeated examinations. In the 18 cases in the present series, the mothers gave a history of from 28 to 32 weeks of gestation in 12, of from 32 to 36 weeks in 2, of from 36 to 40 weeks in 1 and of 40 weeks in 3.

Although most of the patients were early premature infants, some were born at term. The ocular and cerebral disease occurred at birth or shortly after birth in the mature infants in the same manner and with the same severity as in the premature infants. The disease is frequently noticed later in premature infants than in mature infants because under the conditions of survival in an incubator the eyes are not observed or examined.

Causes of Prematurity.—The precise etiologic factors influencing premature termination of pregnancy may be difficult to determine. Toxemia of pregnancy, in 3 mothers; multiple pregnancy, in 3; uterine bleeding, in 2, and premature rupture of the membranes, in 1, were the precipitating causes tending toward prematurity. On 1 of the mothers with toxemia of pregnancy a cesarean operation was performed.

The mothers were free of known syphilis and other infectious disease. In 1 woman the uterus was histologically normal. The placentas were not diseased in the 9 mothers from the Chicago Lying-In Hospital. The condition of the placentas of the other mothers was unknown. The cause of prematurity in the other 8 cases could not be determined in spite of careful examination of good hospital records and discussion of the cases with the obstetricians. A point of inquiry may be raised on the number of cases of prematurity without cause. The question of habitual miscarriage, numerous pregnancies at short intervals, undernutrition of the fetus with premature expulsion and induced labor does not seem to arise here, although these points were investigated. It is possible that the disease causing cerebral and retinal dysplasia may tend also to cause prematurity, but there is no direct evidence except the frequency of this disease in premature infants. Seemingly, there is no specific disease of the uterus or of pregnancy associated with the dysplasia.

Diseases of the Mother.—Since the prenatal and neonatal appearance of encephalo-ophthalmic dysplasia indicates that the mother may transfer the disease or the effects of disease to the fetus, a search was made for diseases of the mother. One mother had moderately severe essential hypertension; 3 had toxemia of pregnancy; 1 apparently had received treatments for syphilis; 1 had a cough and rapid loss of weight, and 12 had no disease. The Wassermann reactions of the mothers were negative. The blood counts were normal. There was no clinical evidence of lymphogranuloma venereum. The mothers of the patients who were born in 1943 and 1944 had no symptoms or signs of rubella or other exanthems during pregnancy. Unfortunately, questions to gain evidence on the presence of atypical virus pneumonia, ornithosis or psittacosis in the early months of pregnancy were not asked. All histories of colds, influenza, sore throat and cough in the patients were too vague to be of use as possible antecedents. It was believed that the clue to the cause of the disease was in the history of the mother in early pregnancy, but it was not found because of lack of a good method of attack. In spite of the negativity, it should not be permitted to be forgotten, as it may have a definite bearing on the origin of the disease.

Neonatal Clinical Symptoms.—An attempt was made to correlate the neonatal clinical symptoms, such as cyanosis, jaundice and asphyxia,

with encephalo-ophthalmic dysplasia. Four infants had no unusual symptoms. One (case 10) of these 4 infants, a full term child, began to have convulsions after the age of 2 months and later died with a condition diagnosed post mortem as bronchopneumonia, cerebral agenesis and ocular dysgenesis. Another (case 14) of these infants, born of a full term pregnancy, was observed to have retinal masses in each eye within two weeks of birth. Later, according to the diagnosis from post-mortem examination, the child died of pneumonia and congenital hydrocephalus. The third child (case 11), an early premature infant, was born in another hospital, where the records showed no evidence of unusual symptoms, although the child was kept in an incubator. This infant was blind at birth and now is mentally retarded. The fourth child (case 2) of this group, an early premature infant, had retinal masses in each eye, which were first observed six months after birth. The child was normal at the age of 4 years except for blindness. There was no known factor in delivery of the child and no neonatal symptom or sign indicating the cause of the dysplasia in these 4 children.

One infant, born by cesarean section at a previable age, had neonatal anemia with weakness and little vision.

Seven infants were cyanotic after birth. The ratio of 7:18 was about the same (53:102) as that attained by Hess.[8] Three of the 7 infants were cyanotic just after birth and recovered easily with oxygen treatment. The cyanosis of premature infants is generally related to atelectasis. The 4 infants with recurrent cyanosis probably had intracranial hemorrhage. Of these 4, 1 (case 1) died with hydrocephalus four years later. One (case 3) died of enteritis at 4 months of age. The brain histologically was normal. Another (case 4) was admitted to an institution for feeblemindedness at the age of 6 years. The fourth had hemiparesis and cerebral agenesis. Two infants (cases 5 and 17), who were jaundiced several days after birth are living and well. Of 2 other infants with jaundice and recurrent cyanosis, 1 (case 9) with intracranial hemorrhage died at the age of 4 months with a condition diagnosed as congenital hydrocephalus and lissencephaly, and the other (case 7) was healthy and active mentally at the age of 7 years.

One child (case 15) had delayed respirations at birth. At the age of 4 months the child appeared to be normal mentally.

The histories in this small series unexpectedly showed no relationship of asphyxia, cyanosis and jaundice to hydrocephalus, severity of mental retardation and cerebral agenesis except in the infant with severe intracranial hemorrhage (case 9).

Congenital Anomalies.—The congenital anatomic anomalies were few, but they are not significant. Four infants possessed these maldevelopments. There were bilateral talipes equinovarus, hemangioma of the occiput and chest, supernumerary toes and umbilical hernia.

Other Possible Causes.—A further search for the origin of the disease was made. Rubella and similar exanthems of the mother in the first trimester of pregnancy were considered for some of the infants born in 1943 and 1944, after the reports by the Australians.[9] The cases at the University of Chicago Clinics in which the mother had rubella were excluded from this report. The symptoms and signs in these cases were the same as in previous reports. They were congenital cataract, low tone deafness, mental retardation, wide ductus arteriosus, defective interventricular septum and dental dysplasia. These signs are not those of neonatal encephalo-ophthalmic dysplasia.

The Rh factor was determined in 1 case, but there was no incompatibility between the blood of the mother and that of the child. There was no history or evidence of fetal erythroblastosis in the children of any multiple pregnancy.

Light as a factor has been considered by some ophthalmologists and pediatricians. Since 3 infants were born with the disease and 2 others probably had the disease from birth, there is little reason to suspect light as causing the damage to eyes in utero. Whether or not it is an additional factor after birth is still doubtful.

A toxic causation was investigated in a few late cases, but no history of poisoning with alcohol, lead, carbon monoxide, mercury, arsenic, apiol, quinine or tobacco was obtained.

One mother was examined and tested for brucellosis, but there was no indication that she had the disease.

Except for 1 case with probable treatment for syphilis and gonorrhea before pregnancy, there was no history of syphilis. All Wassermann reactions were negative.

Although there were no symptoms of toxoplasmosis in any mother and infant, the blood of 1 infant gave a negative reaction to the protective test. The pathologic sections of the brain and eyes after death showed no toxoplasmas.

In spite of the absence of any history of obvious symptoms of other virus diseases, it was unfortunate that there was no available method under the present conditions for testing the mother and child for the presence of the viruses causing atypical pneumonia, psittacosis and ornithosis. A virus infection was believed to be a possible cause of the disease.

Chronologic Appearance.—The time of the first appearance of encephalo-ophthalmic dysplasia has an important bearing on the etiologic and pathologic features of the disease. If cases 9 and 10 are taken

9. Swann, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. A.: Congenital Defects in Infants Following Infectious Disease During Pregnancy, M. J. Australia **30**:201, 1943.

as illustrations of the earliest form of the disease, then the pathologic process begins in the first few months of pregnancy. In case 9 the postmortem diagnosis was bronchopneumonia, aplasia of the cerebral cortex and cerebellum, cerebral agyria, multiple heterotopias, congenital hydrocephalus, persistent hyaloid artery, congenital cataract, coloboma of the disk, retinal gliosis of the right eye and buphthalmos, congenital cataract and retinal gliosis of the left eye, and in case 10, bronchopneumonia, cerebral agenesis with multiple heterotopias and cyst of the cerebellum and bilateral retinal dysplasia. These changes occurred early in fetal life. In about the fifth week of fetal life the corpus callosum is formed. In both cases the agenesis of the corpus callosum was determined before the fifth week of embryonic life. After about the third month of embryonic development the cerebral gyri began to take their form. In case 9 the brain was agyric; in case 10 microgyria was present. In both cases the cerebellar aplasia probably was determined later than the agenesis of the cerebrum. The factor producing the subarachnoidal anomalies also was in effect after the second month of embryonic life. The hydrocephalus in case 9 was probably related to failure of development of the subarachnoid space. The heterotopias represented a further differentiation after a temporary arrest. Some tissues not differentiating further remained hypoplastic, and the revival in growth of tissue resulted in dysplasia or hyperplasia.

The ocular maldevelopment in case 9 occurred probably through arrested development of the initial retinal differentiation at the embryonic age of 3 months. The right eye was microphthalmic, and its retina showed dysplasia. The retina of the left eye was also maldeveloped and later was made atrophic in part by secondary glaucoma.

In case 8 the eyes and brain were affected by the sixth month of pregnancy.

General Etiologic Factors.—Many probable general causes for the disease exist (Corner [10]). The problem may be summarized as follows:

1. Irregular fertilization may cause incomplete segmentation and death of the egg.

2. There is no evidence that this disease is related to a genetic defect.

3. It is possible, but not probable, that there is a relationship to a nongenetic constitutional defect. A comparable disease is mongolism. However, at present there is no good method of attack on this problem.

4. Delayed transportation of the egg through the oviduct frequently results in ectopic pregnancy and prominent defects. However, tubal pregnancy is not a factor in this disease.

10. Corner, G. W.: Ourselves Unborn, New Haven, Conn., Yale University Press, 1944, p. 108.

5. A failure of the hormone system causes early death of the embryo in animals. This effect has not been definitely observed in man.

6. A mechanical disorder of the uterus resulting in crowding of the embryo generally causes miscarriage at the end of the second or the third month.

7. Nutritional deficiencies, unless they are severe, have little effect on the embryo but a definite effect on the mother.

8. Infection of the genital tract tends to prevent fertilization and implantation of the egg.

9. Toxicity of the environment may cause maldevelopment. Roentgen radiation, radium, lead intoxication and the Rh factor are not apparent factors in the disease under discussion. Generally, a toxic reaction sufficient to affect the embryo affects the mother, and the cause of toxicity can be determined. Local intrauterine toxicity as a cause of developmental defect is difficult to prove.

10. The embryo may be infected with any of many organisms. Syphilis and smallpox are well known diseases of the fetus. Rubella, or German measles, recently was found to affect the embryo. If the mother had rubella during the first two months of pregnancy, the infant was frequently born defective. The abnormalities were congenital cataract, microphthalmos, deaf-mutism, patent ductus arteriosus, hypoplastic teeth, microcephaly and mental retardation. There is good reason to believe that the virulence of the virus of rubella may have changed and that the effect of this virus has not been recognized. The cases with a history of the mother's having rubella or symptoms of rubella were not included in this series. It is possible that another virus may be the cause of encephalo-ophthalmic dysplasia.

SYMPTOMATOLOGY

OCULAR SYMPTOMS

The study of ocular symptoms in the 18 cases gave information on diagnostic errors, on the differential diagnosis and on the chronologic features and clinical variation of the disease.

Time of Onset.—The probable time of onset of the disease was difficult to determine in some infants because the early symptoms were not observed, the abnormalities were not investigated and the eyes were not examined, or, if they were, the examination was inadequate. In cases 8, 9, 10, 11, 14 and 17 the eyes were affected before birth. According to the histologic observations on the eyes in cases 9 and 10, the disease was evident in the early fetal stage, and in case 8 the retina had been detached and then reattached before birth. In case 17 the retinal maldevelopment which was disclosed by clinical observation was similar to that of falciform fold and stalks of the retina, which is an early embry-

onic defect. In the other cases, 11 and 14, vision was poor at birth, and the retinal mass was seen just after birth. In 4 cases the retinal defect was probably present before the first few weeks of life; in 3 cases, before 2 months of age; in 2 cases, before 3 months of age; in 1 case, long before 6 months of age, and in 2 cases, long before 9 months of age. If the symptoms are discovered late, the disease is usually mild, and the early stages are overlooked. Terry noted that the retinal disease in his cases was always visible before 6 months of age.[1f]

Time of First Observation.—The time of first observation of the ocular defect varied remarkably for a serious disease which occurs at birth or in the early weeks of life. In 3 cases the defect was noticed at or near birth; in 2, in the first month; in 3, from the first to the second month; in 3, from the second to the third month; in 1, from the third to the fourth month; in 4, from the fourth to the sixth month, and in 2, from the sixth to ninth month. In almost every case the disease was far progressed. The time interval between the initiation of the disease and the time of detection is related to the lack of training in ophthalmoscopy in medical schools and the lack of habitual use of the ophthalmoscope in medical examinations.

The ocular symptoms were usually missed by the physician either because no examination was made or because it is difficult to examine the eyes of recently born infants. This also explains why retinoblastoma is often not observed until the mother notices an ocular defect. The mother was the first observer of an ocular defect in 5 cases; the pediatrician, in 7 cases, commonly because of careful routine examination; the obstetrician, in 3 cases, and the family physician, in 3 cases.

First Prominent Symptoms.—The most prominent symptoms noticed by the first observer, mother or physician, were: blindness, in 14 eyes; retinal mass, in 10 eyes (by the physician); large size of the bulb, in 3 eyes; small size, in 1 eye; white pupils, in 2 eyes, and yellow pupils, in 2 eyes. In 4 eyes no abnormality was noticed. The blindness was often discovered at home when the mother cared for the child. It was apparently not detected by the nurses when the infant was in the Hess bed.

First Tentative Ophthalmic Diagnosis.—In few cases was the first tentative diagnosis the same as the final diagnosis. One reason was that only an examination with the child under general anesthesia was satisfactory. At first the tendency was to consider the retinal mass a retinoblastoma. Later, after more experience, a different conception of the retinal mass was obtained. In 21 eyes the diagnosis was retinoblastoma; in 6, retrolental fibroplasia; in 4, myopia; in 3, pseudoglioma, and in 1 each, atrophy of the optic nerve, microphthalmos, retinal detachment and secondary glaucoma. In 1 eye the disease was missed.

Bilaterality.—In every case the disease was bilateral. In 12 cases bilateral retinal detachment occurred. In 3 cases unilateral retinal detachment with atrophy or dysgenesis of the retina and optic nerve was evident. One case of bilateral retinal gliosis was seen, and 1 case each of bilateral retinal hypoplasia and bilateral congenital retinal folds was found.

The retinal detachment in one eye and the dysplasia of the retina in the other eye gave evidence that the bilateral retinal dysplasia probably belonged to the same group of defects. The early retinal gliosis was perhaps based on different embryonic timing of the same disease process. The congenital retinal folds were part of a similar process. These eyes showed the various possible forms the disease may take. However, in no case was one eye free of disease.

Position of Hands.—The position of the back of the hands over the eyes to avoid light, which was mentioned by Terry,[1] was characteristic in those infants who were unaccustomed to bright light and in whom the retinal detachment was in the early stages. It was not unusual for the infant to act in the same manner when it was photophobic to light on the iris during mild irritative iritis or when it was suffering pain from the secondary glaucoma or the induced glaucoma which arises from crying.

Vision.—Vision ultimately was decreased or totally lost in all cases. In the eyes with congenital myopia and retinal dysplasia but without detachment vision was generally never above perception of shadows and movements and of light in space. The child often misled the examiner by detection of objects by smell and not by sight. In 1 case the child recognized the odor of the father's leather coat and would turn toward the source of the odor. Response to the local heat of a light gave misinterpretations of vision. Infants with fixed congenital retinal folds and stalk or infants just before detachment of the retina or with partly detached retinas noted the direction of the light. A few had vision for larger forms. In all cases of detachment vision was reduced in time to light perception or became nil.

Ptosis.—Ptosis was noticeable in 5 infants. In 4 it was unilateral and in 1 bilateral. Of the infants with unilateral ptosis, the defect was on the left in 3 and on the right in 1. In all cases the ptosis was related to the disease, for it occurred only with microphthalmic eyes, with the eye of smaller size and with more severe disease. It could not be definitely associated with the intrauterine position of the infant or with method of delivery. Endophthalmos seemed to be apparent in 1 of the infants with ptosis. Each eye was microphthalmic, and the smaller eye appeared to be endophthalmic.

Strabismus.—The external ocular movements were unrestricted in all cases. In infants totally blind at birth the movements remained irregular and were not conjugated. If light perception persisted until just after birth in one eye only, the conjugation was poor. If light perception persisted a few weeks after birth, the movements were roving and inconstant but conjugated. In 4 infants the eyes showed occasional convergence, and in 1 the left eye turned in 20 degrees. In 1 infant slight paresis of the left external reactus muscle disappeared when he became older.

Microphthalmos.—The size of the bulb was difficult to determine in a restless infant. It was estimated by measuring the diameter of the cornea; by comparison of the size of one eye with that of the other and with the size of normal eyes of infants of the same age, and by comparison of the enucleated eyes with normal eyes. The transverse diameter of the cornea was estimated in 27 eyes. Microphthalmos was evident bilaterally in 8 cases and unilaterally in 4 cases. In 5 cases the size of the eyes was not abnormal. In the 5 cases of myopia the retinas were at the upper limit of normal size or were larger than normal eyes of infants of the same age. Early, long-continued detachment occurred with small corneas and small eyes. Early and pronounced glaucoma, usually of long duration, gave rise to a large globe. One globe was large at birth (case 9).

Synechias.—The anterior chamber was shallow in 22 eyes and collapsed in 8 eyes. The decrease in depth of the chamber occurred with the retinal detachment and once with retinal dysplasia associated with myopia.

Iridic synechias are common to the eyes with this disease, particularly those with detached retinas. Anterior synechias were observed clinically in 4 eyes and were not noted in many eyes with shallow, collapsed anterior chambers. Five eyes were observed pathologically to have anterior synechias which were not noticed clinically. In 1 eye a particular effort was made to find anterior synechias clinically, but they were seen only after section.

Pupillary Reactions.—The pupillary reaction to light before retinal detachment was apparently active in almost all eyes. After the detachment started, the pupils became sluggish in reaction and later became fixed. The fixation was the result of posterior synechias. In 5 eyes with little or no pupillary reaction to light no posterior synechias were observed clinically, and the irises were probably sticky. In these eyes the pupils dilated with atropine. The pupils in the eyes with retinal gliosis, dysgenesis and myopia became fixed early. In the 18 infants, 24 pupils became fixed, 6 showed some signs of reaction, and the remainder were not closely observed.

Glaucoma.—The abnormally high intraocular pressure was determined with difficulty. In 9 eyes of 5 patients there were signs of glaucoma. The tension, which, when taken, was estimated either by the Schiøtz or by the Souter method while the child was under ether anesthesia, was often subject to misinterpretation. A thin cornea, small eye, collapsed anterior chamber, straining child and lack of a standard for infants were factors which prevented the use of instrumental methods. The bulbar conjunctiva became reddened in 3 eyes with severe glaucoma. Other such eyes often were redder than usual after crying, but this reaction may be related also to mild irritative iritis present with the detached retina. However, reddened eyes were not common with glaucoma. A fugitive corneal haziness in 3 eyes was caused by glaucoma. This sign was probably overlooked in many other eyes, or the infant was not seen at the proper time.

At some stage of the disease increased intraocular tension was obtained in the clinic in 9 eyes, either by tactile or by instrumental measurement. These eyes showed injection of the conjunctiva and a steamy cornea with the rise in intraocular pressure. In some eyes the glaucoma was observed only when the infant cried. The glaucoma generally followed the posterior synechias or intraocular hemorrhages. It lasted for weeks or months, and then the eye tended to become softer. In case 9 the left eye had a congenital hydrophthalmos but not buphthalmos. The congenital incomplete development of the filtration angle was an added factor in glaucoma. Some microphthalmic eyes were of average size because of the glaucomatous pressure.

Fetal Vascular System.—Persistent pupillary membranes and vessels were more commonly present in the eyes of the early premature infants shortly after birth and in the eyes with marked malformations or retinal detachments in full term infants. Vessels of the iris extended over or onto the pupillary opening in 4 eyes after, but not before, the retinal detachment. They were not seen in several eyes.

The hyaloid artery was not evident in the premature eyes. If vascular remnants of the hyaloid artery were present, they could not easily be found in the detached retinas on gross examination. The hyaloid artery was not observed in the microphthalmic eye, in which it was later seen in section, because of the obscuration from an anterior hyaloid membrane.

A vitreous membrane was believed to be present in 4 eyes. The membrane was not positively identified in sections in 1 eye and was related retinal folds in another. In 1 eye (case 9, right eye) it was dense and was seen to extend from the ora serrata in the sections.

The white and black dentate processes of the ciliary body were observed in 4 eyes. Two of these eyes had retinal folds. Unfortunately, search for dentations was made only in a few late cases. This

observation, first noted by Lane [21] and later by Terry, was an aid in diagnosis of non-neoplastic disease.

Lens.—The lens was clear in nearly all eyes. In the infant with gliosis, the lens of one eye was slightly hazy, and the other was believed to have a yellow nodule near or in the posterior cortex. Another lens showed a few translucent cortical striae. In an eye with retinal folds extending to the posterior capsule, the lens was cataractous at the place of contact, but the other lens seemed clear. In 1 infant with retinal detachment both lenses became hard cataracts. The other lenses, when displaced toward the cornea and when in eyes with glaucoma of long duration, became cloudy, but the haze of the cornea prevented close observation.

Retina.—The most common feature was the retinal disease. The varieties of disease have been given in the discussion of its occurrence in the eyes. In the eyes with dysplastic, undetached retina, the disk was pale as though atrophic. In some eyes it appeared slightly colobomatous. In highly myopic eyes and in 1 nonmyopic eye the retinal vessels seemed smaller than normal. In 1 eye they were crowded to the side of the disk. The fundus reflex was not so brilliant and red as normal. The macular reflex was absent. In 2 eyes white circular areas, rimmed lightly with melanotic pigment, were scattered around the disk. They tended to increase slowly in size. Retinas with congenital folds have been described by Ida Mann [11] in numerous articles.

The retinal detachment was seen as a solid, roughened, grayish red mass of retina. The roughened retina was quite characteristic in the early process of detachment. The detached mass came forward like a funnel. Occasionally one side was more prominent than the other. The retina then appeared detached on one side, and on the other the reflex of the choroid gave a picture of a blurred reddish retina. If the detached retina became thin, the red choroidal reflex was seen. The retinal vessels disappeared in the center of the roughened retina in cases of total detachment. In a few eyes hemorrhages occurred in the retina and appeared as a dark red, brown-black mass just behind the lens. If a larger hemorrhage occurred, the whole retina was suddenly crowded against the lens, which, in turn, was pushed toward the cornea. If the retina was partly detached, examination by means of the slit lamp or fine beam and proper magnification, with the patient under general anesthesia, showed the dentate processes of the ciliary processes. The long processes were white and fused with the light-colored detached retina. The spaces between the dentation were black in the early stages of the disease; after the retina atrophied the spaces showed the red choroidal reflex.

11. Mann, I.: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937.

GENERAL NEUROLOGIC SYMPTOMS

There were no special pathognomonic symptoms of the neurologic disease. The two common symptoms were hydrocephalus and, especially, mental retardation. The mental retardation was related to lack of cerebral development and to the effects of hydrocephalus, which in 1 case at least was associated with the anomaly of the arachnoid membrane. The basal ganglions, brain stem and spinal cord were not involved in the dysplasia; if they were affected, their disease probably had a different origin.

Hydrocephalus, Microcephalus and Cerebral Agenesis.—Hydrocephalus occurred in 4 cases. Blockage of the intercommunicating system was the main cause. One infant (case 8) was known by roentgenographic examination to have extreme hydrocephalus in utero and of necessity was delivered by cesarean section. The child died one day after birth. At autopsy the whole brain collapsed to an unrecognizable mass.

In case 9 extreme congenital hydrocephalus and a large intracranial hemorrhage were present at birth. In this case the blockage was related to congenital maldevelopment of the arachnoid structure. Presumably, in the other cases the hydrocephalus was due to a similar maldevelopment.

In case 14 signs of hydrocephalus were first noticed at the age of 1 month. Trepanation showed a thin cortex and dilated ventricles secondary to obstruction of the ventricular system. This was confirmed at autopsy at the age of 1 year and 8 months.

In case 6 the hydrocephalus began to be obvious six weeks after birth. It became extreme and caused the death of the infant at the age of 5 months. At autopsy fibrous adhesions were observed to block the aqueduct.

In the 2 infants with heads of normal size at birth the ventricles may have been dilated before birth, for the intrauterine pressure tends to prevent expansion of the skull and the head may enlarge in the following months. One infant showed bulging fontanels and separation of sutures only when the dehydration was overcome. The yellow fluid in the ventricles in case 14 was probably due to rupture of small veins by the traction arising from the hydrocephalus.

With hydrocephalus occurred the usual symptoms, such as convulsions, vomiting, cyanosis, lethargy and spasticity. Many of the other common congenital defects associated with congenital hydrocephalus, i. e., meningocele, porencephaly, spina bifida and cranium bifidum, were not present. In 2 of the 4 infants with hydrocephalus there was no retinal detachment but dysplasia of the retina and atrophy of the optic nerve. In 2 infants the retinas were detached. As the roof of the orbit was depressed, the bulbs were pushed downward and outward.

Cerebral agenesis was diagnosed in 3 cases (12, 13 and 16), and microcephalus with hydrocephalus, in 1 case (10). The same pathologic processes which led to hydrocephalus in other cases apparently produced cerebral agenesis and the secondary microcephalus in these cases.

Other Neurologic Symptoms Not Pertaining to the Disease.—Other neurologic symptoms not particularly related to the disease were cephalohematoma, subdural and subarachnoid hemorrhage (case 9), hemiparesis (case 13), spastic quadriplegia (case 16) and cerebral spastic palsy (case 18).

Mental Retardation.—Mental retardation was noted in almost every infant. Ten infants were definitely retarded, and 3 were probably retarded. In 2 infants the mentality could not be determined. Two infants were normal. Psychometric tests on 5 children indicated low mentality. It was impossible to give suitable tests to many of the children because of loss of eyesight, the effect of the protective environment at home, the age of the infant and lack of suitable standard methods of testing, which are yet to be developed.

The tests for mental retardation were difficult to apply to these children. The circumstances of their life were different from normal infants of their age. Lack of vision, protective environment and prematurity are relatively unknown factors in testing. There is little experience or information on which to base a judgment as to the mentality of these infants. A careful history and repeated intelligent observation of the child's behavior gave a better idea of the mentality than testing.

The Kuhlmann intelligence rating which covers the period from 3 months to 2 years of age was determined for a few of the most adaptable children by an experienced child psychologist. In case 1, the Kuhlmann intelligence quotient was 41; in case 11, 39, and in case 10, 5; in cases 12 and 18 the mentality was low grade but could not be estimated numerically.

The Gesell tests were quite useless here for intelligence rating, for they depend mainly on motor reactions. It was surprising that the blind infant in case 1 had a Kuhlmann intelligence quotient of 41 at the age of 3 years, was considered mentally normal two months later by expert state psychologists and psychiatrists and then died within two months of a "brain tumor."

Final Disposition.—Encephalo-ophthalmic dysplasia was more than static blindness and mental retardation after the age of 6 months. In some infants it was progressive, and in others it was arrested or partly arrested. It would not be surprising if hydrocephalus should develop later in childhood in infants who do not show it. All these children should be followed for a lifetime.

Seven infants with the dysplasia have died. Autopsies showed that 1 died at birth of hydrocephalus; 1, at 13 weeks of age of acute enteritis; 1, at 4 months of pneumonia; 1, at 5½ months of hydrocephalus; 1, at 1 year 5 months of bronchopneumonia; 1, at 1 year 9 months of pneumonia, and 1, at 3 years 5 months of a "brain tumor." Three infants were placed in institutions for the feebleminded. Their ages in January 1945 were 1, 3½ and 7 years. Three infants, aged 1½, 2½ and 5½ years, are feeble physically and retarded mentally. Three infants, aged 5½, 7 and 5½ years, are healthy. The condition of 2 infants, aged 2½ and 3½ years, is unknown at present.

DIFFERENTIAL DIAGNOSIS

The retinal disease most likely to be confused with this disease is retinoblastoma and pseudoglioma. The other diseases which may simulate encephalo-ophthalmic dysplasia are relatively easy to diagnose.

Retinoblastoma.—If there is reasonable doubt whether or not a retinoblastoma is present, a decision must be made on the removal of the eye. However, there are certain common characteristics of encephalo-ophthalmic dysplasia which help to differentiate between the two diseases. They are: (1) prematurity, (2) congenital defective vision, (3) bilaterality or ocular disease, (4) congenital retinal anomalies, (5) microphthalmos, (6) central radiating blood vessels on the rough surface of a central retinal mass, (7) prominent dentate processes of the ciliary body, (8) recurrent retrolental hemorrhage and (9) early mental retardation.

The contrasting signs and symptoms of retinoblastoma are: (1) roentgenographic evidence of ocular calcification; (2) disseminated foci of tumor in some eyes; (3) occurrence usually later in life; (4) occasional evidence of familial tendency; (5) generally unilateral occurrence, and (6) masses with typical smooth, glistening surface.

Metastatic Enophthalmitis.—A history of meningitis, otitis media, scarlet fever, measles, mumps or other infectious disease is related to the retinal detachment or mass behind the lens. In cases without a history of infection, the pain and redness of the eye, the photophobia, fever, rash, convulsions, spasticity, vomiting and coma are suggestive of metastatic enophthalmitis.

Tuberculosis.—A tuberculoma is generally unilateral. The infant will show other signs of tuberculosis, and the tuberculin test gives a positive reaction. Exposure of the child to tuberculosis will be evident from the presence of the disease in some one who is in close contact with the child.

Syphilis.—Congenital syphilis of the eye is associated with other physical signs in the mother and child. The Wassermann reactions of the mother and of the child are often positive.

Rubella.—Detachment of the retina has occurred with rubella. It may be impossible to obtain a history of rubella in the mother in early pregnancy. Lenticular opacities are usually visible before any retinal changes are seen. The infant may have a large ductus arteriosus, deafness to low tones, mental retardation and dental aplasia.

Retinal Gliosis.—Gliosis of the retina resulting from hemorrhages is extremely rare in infants. The lesion tends to be localized as a clearcut, permanent retinal plaque. Gliosis of the entire retina with other signs was found in 1 case of encephalo-ophthalmic dysplasia.

Retinal Folds.—The retinal folds which were described by Mann [11] are commonly familial. They are a result of a congenital maldevelopment of the vitreous and retina which is not progressive and which may occur in one or both eyes.

Persistent Hyaloid Artery.—Some of the points of difference in eyes with persistent hyaloid vascular systems are unilaterality, absence of detached retina, nonprogressiveness of the process and absence of mental symptoms and history of prematurity.

TREATMENT

The medical and surgical treatment of retinal dysplasia is unsatisfactory. The instillation of solutions of pilocarpine is perhaps not the proper method to reduce the congenital secondary glaucoma in the presence of posterior synechias. The application of solutions of atropine to overcome the formation of posterior synechias and secondary glaucoma tends to cause greater blockage of the immaturely developed filtration angle. The use of radium or roentgen radiation to reduce vascularization and proliferation of glial and mesodermal connective tissue has had questionable success and may actually stimulate tissue proliferation.

In most cases with retinal detachment an operation, such as trepanation for the reduction of the intraocular pressure, may not give relief from the glaucoma. There is always the question whether or not retinal and retrolental hemorrhages will be more frequent and severe when the pressure is reduced. Since the iris and the ciliary processes are involved in the disease, the operation may be useless and may result in more damage to the eye. In the cases with secondary glaucoma without retinal detachment a trepanation may be a valuable method of treatment.

In the case of an eye which has vision and which has a congenital cataract with congenital retinal folds, retrolental and ciliary membranes or anomalous vascularization which is fixed and not undergoing changes, an operative procedure on the membranes or vessels of the lens, to give sufficient opening through the pupil, may be considered. The technical details for each operation must be planned before surgical attack. Cata-

ract extraction in eyes with total retinal detachment is useless. Of course, surgical correction of the massive retinal detachment is as yet impossible.

If the eye is red and painful from uncontrollable secondary glaucoma or if there is reasonable doubt concerning glioma, an enucleation of the eye arises as a problem for decision. In some eyes the high intraocular pressure decreases as the retina atrophies.

SOCIAL SIGNIFICANCE

Medical.—If children with this defect are affected in utero by a specific disease of the mother during early pregnancy, it is important to determine the disease which produces the maldevelopment. The question would then arise whether the pregnant woman affected with the disease should have her pregnancy terminated to prevent the chance of birth of a defective child. Whatever the cause of the dysplasia, the disease is sufficiently frequent and severe to merit attention to prevention. A blind, mentally retarded child is a social burden.

Social.—It is important to determine the mental status of the infant early by competent and experienced child psychologists. If the child is feebleminded, he should be committed to an institution as soon as it can be done. If the infant or child is at home or in a similar environment, the special protective reaction of the mother, relatives or attendants may greatly hinder the development of the mind and may also create behavior problems. It is difficult to judge mental retardation in such circumstances. A congenitally blind healthy child will respond to proper social treatment in a remarkable manner.

Legal.—There is good probability that some of these infants may be adopted by foster parents. The laws concerned with adoption are considered to give the most irrevocable contract known legally. If an infant with this disease is legally adopted, the adoption later cannot be annulled. The adoption of a child is an act of faith and hope in any case, in spite of the best preadoption examination and investigation of the child and his relatives. A happy future for the perfect child is expected, but not guaranteed. Except in cases of severe disease, it is unlikely that the cerebral symptoms in a young infant will be noticed in examination by the average physician. If the retinal lesion is not obvious, or if it develops after the first few months of life, the ocular defect may not be observed until after adoption. The examination of an infant under 1 year of age is restricted by the lack of detailed knowledge and standards, so that it cannot compare with a similar examination performed later in life. Mental tests on infants are notoriously unsuccessful. Mental retardation, unless it is extreme, is difficult to detect, as evidenced by this series of cases.

A legal case of this kind has been presented in court. The infant was considered to be healthy by a physician before adoption. Shortly after adoption the infant had difficulty in seeing. On examination the child was found to have the retinal dysplasia. The foster parents of the child are now suing for annulment of the adoption.

SUMMARY

Eighteen cases of congenital encephalo-ophthalmic dysplasia of unknown origin are described. The neuroectodermal disease was more commonly found in premature infants and in single infants of a multiple birth. The common neurologic signs were mental retardation, microcephalus and hydrocephalus. In some cases the brain, on histologic examination, showed cerebral and cerebellar hyperplasia, hypoplasia and agenesis, heterotopias and internal hydrocephalus. Clinically, the ocular disease rarely occurred without neurologic signs of involvement of the brain when the child was examined after the age of 4 years.

The ocular signs were loss of vision, ptosis, enophthalmos, microphthalmos, strabismus, retinal detachment, postlental masses, retinal atrophy, gliosis, recurrent retinal and vitreous hemorrhages, anterior and posterior synechias, secondary glaucoma and cataract. The hyperplasia, hypoplasia and dysplasia of the retina and colobomas of the choroid and optic nerve were accompanied with malformations of the associated mesodermal tissue.

No method of treatment was found to prevent or to cure the disease.

The common disposition of a child with the severe form of the disease was commitment to a state institution for the feebleminded or to an institution for the blind. Death from intercurrent infection frequently occurred.

950 East Fifty-Ninth Street (37).

ETIOLOGY AND TREATMENT OF BLEPHARITIS

A Study in Military Personnel

PHILLIPS THYGESON, M.D.
SAN JOSE, CALIF.

BLEPHARITIS is a chronic inflammation of the lid border. It can be divided into two general types: (1) the squamous type, characterized by hyperemia of the lid border with dry or greasy scales; and (2) the ulcerative type, characterized by the development of small pustules involving the follicles of the cilia and leading to the formation of small ulcers. Conjunctivitis and superficial keratitis commonly accompany both types.

Blepharitis is the most common external ocular inflammation seen in military personnel and is an important cause of disability, both in itself and as the source of a number of disabling complications. It is of distinct military importance because the symptoms characteristic of the moderately severe and acute forms, which include burning and smarting, epiphora, photophobia and asthenopia, interfere definitely with the efficiency of the soldier. These symptoms appear to be particularly troublesome in air crew members and to be exaggerated during high altitude flying. The complications range from internal and external hordeolums, meibomitis and chalazion to chronic conjunctivitis, marginal ulceration of the cornea and, rarely but importantly, trichiasis and entropion. Although it is not generally recognized, even very mild forms may be the source of chronic catarrhal conjunctivitis. Of relatively minor importance, but not to be ignored, is the cosmetic aspect of the disease. The unsightly scaling, redness and epiphora may constitute a definite morale factor in military personnel.

In many clinics the significance of blepharitis is apparently underestimated, and soldiers complaining of the disease are neglected in the sense that they are often given prescriptions without follow-up care of any kind. Since the most important clinical feature of blepharitis is its chronicity, unsupervised home treatment is almost inevitably unsatisfactory. Determination of the etiologic factor, moreover, is in most cases a prerequisite for adequate therapeutic management, which in any event requires frequent observation and a judicious rotation of procedures in all but the mildest type.

The frequency and severity of blepharitis seem to be definitely increased under tropical conditions. Its military importance was,

therefore, relatively greater in the recent war as a result of the concentration of troops in the South Pacific area.

Textbook discussions of blepharitis have long seemed to me to be regrettably inadequate with respect to both etiology and therapy. In spite of general recognition that the disease is not an etiologic entity, there has been a tendency to consider it a clinical entity to be treated without regard to causative factors.

A survey of the literature reveals that a wide variety of etiologic possibilities have been advanced. The more significant of these are as follows: (1) bacteria, including staphylococci, streptococci and diplobacilli; (2) allergy to various substances; (3) fungi; (4) errors of refraction; (5) seborrhea; (6) animal parasites; (7) vitamin deficiencies; (8) endocrine disturbances, and (9) hereditary predisposition. In his excellent review on blephoritis published in 1929 Aubaret [1] discussed these factors in detail and reviewed the literature adequately to that date. Since then the few etiologic studies reported have been devoted largely to a consideration of the role of pathogenic staphylococci in the disease. The reports of Burky,[2] Allen [3] and Thygeson [4] indicated that toxin-producing staphylococci were probably the most important single etiologic feature and that antistaphylococcic therapy was an improvement over older therapeutic measures.

In undertaking this study, it was proposed to define all possible etiologic factors and to evaluate therapeutic procedures in a series of unselected cases of blepharitis observed in Army personnel. The series presented no unusual aspects other than that the patients were, with few exceptions, young adults. There is every reason, therefore, to believe that the disease as seen in this series is representative of blepharitis in the civilian population. The condition in these cases ranged in severity from the mild, almost subclinical type to the severe, ulcerative type with conjunctival and corneal complications. Of these, 350 were available for complete etiologic analysis, but in a number of cases Army transfers interfered with the completion of therapeutic studies.

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1. Aubaret, E.: Etiologie et traitement des blépharites, Paris, Masson & Cie, 1929; Bull. et mém. Soc. franç. d'opht. **42**:1, 1929; Arch. d'opht. **46**:372 (June) 1929.

2. Burky, E. L.: Studies on Action of Staphylococcus Toxin and Anti-Toxin with Special Reference to Ophthalmology, Am. J. Ophth. **19**:841 (Oct.) 1936.

3. Allen, J. H.: Experimental Production of Conjunctivitis with Staphylococci, Am. J. Ophth. **22**:1218 (Nov.) 1939; Staphylococcic Conjunctivitis: Experimental Reproduction with Staphylococcus Toxin, ibid. **20**:1025 (Oct.) 1937.

4. Thygeson, P.: (*a*) Bacterial Factors in Chronic Catarrhal Conjunctivitis: Role of Toxin-Forming Staphylococci, Arch. Ophth. **18**:373 (Sept.)) 1937; (*b*) Treatment of Staphylococcic Conjunctivitis with Staphylococcus Toxoid: Preliminary Note, ibid. **20**:271 (Aug.) 1938; (*c*) Staphylococcic Blepharitis, Tr. Am. Acad. Ophth. (1941) **46**:265 (July-Aug.) 1942.

Not included in the series were cases of marginal blepharitis seen in connection with such dermatologic conditions as exfoliative dermatitis, pityriasis rosea and herpes simplex. As a minor manifestation of a generalized disorder, the involvement of the lid margin in these cases differed from typical marginal blepharitis in being self limited. Two cases of pityriasis rosea, for example, which were referred by Capt. Morris Waisman, M.C., A. U. S., chief of the dermatologic section of the hospital, showed a squamous type of blepharitis which was obviously part of the widespread, symmetric, patchlike eruption characteristic of the disease. In both cases healing was spontaneous in about six weeks. Two cases of herpes simplex of the eyelids with involvement of the lid margins were also seen, but in both the lesions cleared rapidly without residual blepharitis.

I. ETIOLOGY

Comprehensive clinical and laboratory studies were made routinely in the search for features which might have etiologic significance. The clinical survey included examination of the following associated parts: (1) the scalp, for evidence of dandruff; (2) the face, for infections of the skin, such as seborrheic dermatitis and acne rosacea, and for evidence of seborrhea; (3) the external ears, for otitis externa; (4) the tongue, lips and corneal limbus, for clinical signs of vitamin B complex deficiency; (5) the conjunctiva and cornea, for Bitot's spots and keratinization as evidence of vitamin A deficiency; (6) the cornea, with fluorescein, for evidence of catarrhal infiltration or ulceration and punctate epithelial staining of the type characteristic of staphylococcic infection; (7) the meibomian glands, with expression, to determine the existence of hyperactivity or meibomitis, and, finally, (8) the lid margins, to determine, by means of gross and biomicroscopic observation, the clinical type of the blepharitis (whether ciliary or meibomian, ulcerative or nonulcerative), the type of scales (whether dry, tenacious or greasy) and the condition of the cilia (whether infected or otherwise abnormal).

In addition to this objective examination, the patient was questioned on the following points: (1) duration of the disease; (2) history or presence of known staphylococcic infections, such as sties or boils; (3) dietary habits, with particular reference to vitamin deficiency and to the abnormal use of fats and sweets, and (4) history or presence of pruritus or of other allergic manifestation, such as hay fever, urticaria or eczema, with particular inquiry into the possibility of sensitivity to drugs. All patients who had abnormal vision or complained of symptoms of asthenopia were given refraction.

Laboratory studies included examination of routine scrapings from the lid margins with cultures of the material and cultures of secretions

of the conjunctiva when conjunctivitis was a prominent feature. Conjunctival smears were taken when there was conjunctival secretion or when the history suggested the possibility of allergy. When there was complicating meibomitis, expressed meibomian material was studied for cell content and bacteria. When the patient complained of excessive itching, the slides were examined for conjunctival eosinophilia. Other laboratory procedures included the use of special mediums for fungi and the testing of pathogenic staphylococci for sensitivity to penicillin and sulfonamide drugs. Patch tests were used as an aid in the diagnosis of contact dermatitis.

LABORATORY DATA

Table 1 summarizes the laboratory findings in scrapings from the lid margins and cultures in 350 cases of blepharitis. The scrapings from the lid margin yielded only four significant forms: (1) budding yeast forms, (2) cocci, (3) diplobacilli and (4) polymorphonuclear leukocytes. Diphtheroids, considered of no etiologic importance, were

TABLE 1.—*Micro-Organisms in Scrapings from Lid Margins in 350 Cases of Blepharitis*

	Number of Cases
Budding yeast forms, only	100
Pathogenic staphylococci, only *	130
Hemophilus duplex	4
Mixed yeast forms and pathogenic staphylococci	102
Alpha streptococci	3
Beta streptococci	2
Coliform bacilli	1
Proteus bacilli	2
Normal flora	6

* Coagulase-positive Staphylococcus aureus and Staphylococcus albus.

also usually present. The bacterial cultures yielded only two significant organisms: (1) staphylococci and (2) diplobacilli. Beta hemolytic streptococci were isolated (simultaneously with Staphylococcus aureus) in 3 cases, alpha hemolytic streptococci in 2 cases, a coliform bacillus in 1 case and a proteus organism in 2 cases. Diphtheroid bacilli and isolated colonies of nonpathogenic white staphylococci were also commonly found.

Budding Yeast Forms.—In the scrapings from the lid margin the budding yeast forms, occurring often in large numbers, were by far the most conspicuous finding. They were morphologically identical with similar forms found in dandruff (seborrheic dermatitis) and known as Pityrosporum ovale. Round forms predominated over oval, flask-shaped forms. Cultivation of the organism on beer wort agar was obtained with some difficulty by Capt. Joseph Gots, Sn.C., A. U. S., and, together with other observations on P. ovale, will be the subject of a later communication.

The role of P. ovale in seborrheic dermatitis is still unsettled, but it is believed by some observers [5] to be the primary cause of the disease, with the acne bacillus and Staphylococcus albus acting as secondary factors. Whether or not this will prove to be true, it seems to have been definitely established that large numbers of the organism are invariably found in cases of the disease. To test the usefulness of its demonstration as a diagnostic sign of seborrheic blepharitis, scrapings

Fig. 1.—Pityrosporum ovale in scrapings from the lid margin in a case of blepharitis; × 900.

5. Moore, M.; Kile, R. L.; Engman, M. F., Jr., and Engman, M. F.: Pityrosporum Ovale (Bottle Bacillus of Unna, Spore of Malassez): Cultivation and Possible Role in Seborrheic Dermatitis, Arch. Dermat. & Syph. **33**:457 (March) 1936. Kile, R. L., and Engman, M. F.: Further Studies of the Relation of Pityrosporum Ovale to Seborrheic Eczema, ibid. **37**:616 (April) 1938.

from a series of 25 lid margins which appeared normal on examination with the slit lamp and which had not previously been inflamed were examined for the organism. In 2 specimens only were isolated yeast cells observed. On the other hand, every one of a series of scrapings from 25 blepharitic lid margins, which were negative for pathogenic staphylococci and diplobacilli but with which there was associated seborrheic dermatitis of the scalp, face or external ears, contained large numbers of the organism. It would seem legitimate, therefore, to attach at least some diagnostic value to this finding.

Cocci.—The demonstration in scrapings alone of gram-positive cocci would appear to have little diagnostic significance, since it is not possible by morphologic differences alone to distinguish pathogenic from nonpathogenic staphylococci. Culture study in numerous cases, however, indicated that pathogenic staphylococci are the only cocci occurring in sufficient numbers in cases of blepharitis to be of significance in the examination of scrapings from the lid margins. I therefore now consider the demonstration in scrapings of both gram-positive cocci and polymorphonuclear leukocytes to be a fairly reliable diagnostic sign of staphylococcic blepharitis. It should be emphasized, however, that this finding is present only in severe cases.

Certain diagnosis of staphylococcic infection can be made most reliably by means of blood agar cultures. An attempt has been made in this study to differentiate sharply between pathogenic and nonpathogenic staphylococci on the basis of the coagulase test and mannitol fermentation. These presumptive tests for pathogenicity are now widely used and have been shown to be reasonably trustworthy, with the coagulase test the more valuable of the two. In general, it can be stated that most strains of Staph. aureus are pathogenic and most strains of Staph. albus are nonpathogenic. In table 1 it will be seen that presumably pathogenic staphylococci were recovered from 130 of the 350 cases of blepharitis. Pathogenic staphylococci thus constitute the most important single finding in this series of cases.

It should be noticed that the concomitance of P. ovale and pathogenic staphylococci was observed in 102 cases.

Diplobacilli.—Haemophilus duplex (Morax-Axenfeld diplobacillus) was demonstrated in only 4 cases, but in these it occurred in large numbers and was also demonstrable in smears of the conjunctival secretion. Since this organism is known to be highly parasitic, its demonstration on the lid margin can certainly be considered an indication of its etiologic significance. No polymorphonuclear leukocytes were found in association with the diplobacilli, a finding consistent with the known fact that diplobacilli are not pyogenic.

Other Organisms.—The significance of beta hemolytic and alpha hemolytic streptococci in blepharitis is difficult to evaluate; but as

they are known to attack the scalp and other areas of the skin, it is probable that they are occasionally concerned in blepharitis. The role of beta hemolytic streptococci in impetigo is well known. In the present series alpha streptococci were recovered in 3 cases and beta streptococci in 2.

Fig. 2.—Haemophilus duplex (Morax-Axenfeld diplobacillus) in scrapings from the lid margin in a case of blepharitis due to this organism; × 900.

Coliform bacilli were found in a single case and proteus bacilli in 2 cases. These organisms are occasionally found as probable causal agents in conjunctivitis, but there is no evidence to indicate that they can attack areas of the skin and therefore no reason to attach etiologic significance to these isolated findings.

In view of the frequency of ringworm infections in this geographic area, a special search was made for ringworm fungi in scrapings and cultures from the lid margins. It is noteworthy that not a single case of this infection was found.

ETIOLOGIC TYPES OF BLEPHARITIS

A comparative study of laboratory and clinical findings revealed that only three important etiologic types of marginal blepharitis could be distinguished in this series. These were: (1) blepharitis due to seborrheic dermatitis, (2) blepharitis due to pathogenic staphylococci and (3) blepharitis due to H. duplex (Morax-Axenfeld diplobacillus). Their characteristics are summarized in table 2. There was a high incidence of mixed seborrheic and staphylococcic blepharitis.

TABLE 2.—*Characteristics of the Three Principal Types of Blepharitis*

	Staphylococcic Blepharitis	Seborrheic Blepharitis	Blepharitis Due to Hemophilus Duplex
Seborrhea capitis.....	Occasionally present	Always present	Occasionally present
Associated dermatoses...	Acne vulgaris, rosacea, impetigo, infectious eczematoid dermatitis, sycosis barbae, boils	Seborrheic dermatitis of brows and external ears frequent	Occasionally dermatitis at external nares
Bilateral or unilateral....	Unilateral involvement not uncommon	Always bilateral	Unilateral involvement not uncommon
Ulcerative or nonulcerative	Frequently ulcerative	Never ulcerative	Never ulcerative
Associated hordeolum....	Frequent	Rare or absent	Rare or absent
Associated conjunctivitis	Frequent and often severe	Minimal or absent	Always present
Associated keratitis.....	Punctate epithelial erosions generally present; marginal infiltrates and ulcers common	Absent	Marginal infiltrates and ulcers common
Scales and crusting.....	Hard, tenacious scales, removable with difficulty	Greasy scales, easily removed	Macerated epithelium with minimal scaling
Microscopic examination of scrapings from lid margin	Staphylococci and leukocytes	Budding yeast forms (Pityrosporum ovale)	H. duplex; no leukocytes

Seborrheic Blepharitis.—The following clinical characteristics were present in the blepharitis believed to be due entirely to seborrheic dermatitis: 1. There was always an associated seborrhea capitis, usually of from moderate to severe intensity, with a history of annoying dandruff. 2. An associated seborrheic dermatitis of the brows and external ears was present in a significant number of cases. 3. The blepharitis was always nonulcerative and squamous in character, and the scales were greasy and easy to scrape off. 4. Associated conjunctivitis, if any, was minimal, and in only a few cases was there any punctate staining of the cornea, a feature highly characteristic of staphylococcic infection. 5. The symptoms were always minimal, the patient in many cases being unaware of the presence of the disease. 6. There was

no characteristic association with hordeolum or furunculosis. 7. The disease was characteristically bilateral, no single case of unilateral involvement being demonstrated in this series. 8. The skin of the face usually, though not always, showed evidence of increased sebaceous activity.

In connection with this clinical picture, which could be considered diagnostic without laboratory study in most instances, scrapings from the lid margin always showed budding yeast forms identical with the P. ovale believed to be characteristic of seborrhea capitis.

It should be emphasized at this point that pure seborrheic blepharitis was less common than mixed seborrheic and staphylococcic blepharitis. There was a strong suggestion, in fact, that the principal role of the seborrheic infection was to prepare the soil for secondary staphylococcic involvement, with its relatively severe symptoms and complications. While seborrheic blepharitis is not in itself disabling, its importance as a cosmetic blemish is considerable, the red lid margins and greasy scales being conspicuously unattractive.

Staphylococcic Blepharitis.—The following important clinical characteristics of blepharitis in which pathogenic staphylococci were the only significant findings were noted in this study: 1. Unilateral disease was frequently seen, particularly in cases of recent onset. The disease was often limited to a single portion of the lid margin, moreover, or involved one lid almost to the exclusion of the other. It is noteworthy that symptoms were always more severe when the upper lid was involved predominantly, perhaps because gravity permitted scales and infectious material to fall into the conjunctival sac more frequently. 2. The blepharitis was often ulcerative and was commonly associated with recurrent hordeolums and chalazions. 3. The scales were small, hard, tenacious and sometimes extremely difficult to remove. 4. Associated keratoconjunctivitis was almost the rule. This was sometimes extremely severe and appeared to outweigh in importance the blepharitis which was believed to be its primary focus. In cases of mild keratitis only punctate epithelial staining appeared, principally of the lower halves of the cornea, but in cases of the more severe form there were marginal infiltrates and ulcers, which were always associated with formation of new vessels. 5. Temporary or permanent loss of cilia was a feature of the ulcerative type. 6. Other dermatologic associations were common, particularly otitis externa, impetigo, sycosis barbae and infectious eczematoid dermatitis. Acne vulgaris was frequently present. 7. Symptoms of burning, itching, photophobia and eyestrain were associated with all but the very mildest forms.

The characteristic pathologic pictures of all types of staphylococcic dermatitis were observed in the infections of the lid margins of this series, as follows: 1. A typical eruption of superficial pustular folli-

culitis, characterized by yellow pustules pierced by hairs, was seen in a number of cases. This infection was limited to the upper third of the hair follicles. 2. The lesions of furunculosis were reproduced in the form of hordeolum, usually single, but sometimes conglomerate and affecting the entire lid margin. The pathologic nature of this lesion is abscess involving the deep part of the hair follicle and its sebaceous gland. 3. Sycosis vulgaris, also called barber's itch, was represented. It resembled superficial pustular folliculitis except for its great severity, perifolliculitis with abscess formation developing. 4. The characteristic lesions of impetigo, which may be of either streptococcic or staphylococcic origin or of both were seen on numerous lid margins. The primary lesion is a red macule, which rapidly becomes a flaccid vesicle and eventually a pustule. After rupture the seropurulent exudate dries, leaving thick, honey-colored crusts. Removal of the crusts discloses superficial ulcers. 5. Infectious eczematoid dermatitis was often seen in relation to blepharitis; and the typical eczematoid eruption, characterized by edema, crusting and weeping, was observed on the lid margin proper. The lesions varied from a very mild type, papular or scaly with little infiltration, to an acutely inflamed type with local edema, pustulation and heavy crusting.

On the basis of these observations, one would clearly be justified in describing staphylococcic blepharitis in terms of its dermatologic equivalents, e. g., impetiginous blepharitis, infectious eczematoid blepharitis, furuncular blepharitis and superficial pustular follicular blepharitis. There would seem to be no particular advantage, however, in complicating the present, generally used, classification of ulcerative and nonulcerative staphylococcic blepharitis, which is roughly adequate for clinical purposes.

Blepharitis Due to Hemophilus Duplex.—1. The principal clinical characteristic of this infection was its angular localization, with maceration of the skin at the inner and outer canthi. 2. An associated conjunctivitis was invariable and always prominent. 3. The infection was always superficial, showing no tendency to involve the meibomian glands, and there were no associated hordeolums. 4. The condition was never ulcerative. 5. Punctate staining was rare and, when present, differed strikingly from the punctate staining of staphylococcic infection in showing larger and fewer punctate points. Marginal corneal infiltrates and ulcers did not occur in any of the few cases of this series, but I have seen them in a number of civilian cases.

It should be emphasized that the blepharoconjunctivitis due to H. duplex, while rare in this series, occurs commonly in other parts of the country. I [6] found it to be very prevalent among the Apache

6. Thygeson, P., and Forster, W. G.: Observation on Trachoma of the White Mountain Apache Indians, Proc. Sixth Pacific Sc. Cong. **5**:879, 1939.

Indians of Arizona and to have occurred in almost epidemic form in a mental institution near New York city. No explanation can be given for its low incidence among soldiers at the air field where this study was made in view of the fact that they were drawn from all parts of the United States and were thus unusually representative of the country as a whole.

Mixed Seborrheic and Staphylococcic Blepharitis.—Mixed seborrheic and staphylococcic blepharitis was the second most common type found in the present series. The diagnosis was made on the simultaneous demonstration of pathogenic staphylococci and large numbers of P. ovale in the lesions. Clinically this form resembled the pure seborrheic form more closely than the pure staphylococcic form except that there were usually conjunctival and corneal complications.

The 4 cases of H. duplex blepharitis studied were apparently pure in that no pathogenic staphylococci were found in cultures and no P. ovale in scrapings from the lid margins. In civilian cases, however, I [7] have often seen H. duplex blepharoconjunctivitis mixed with staphylococcic blepharitis, and no doubt it occurs with seborrheic blepharitis.

BLEPHARITIS IN ASSOCIATION WITH OTHER DISEASE

Acne Rosacea.—Blepharitis complicating acne rosacea is a common finding in civilian practice; but, surprisingly, only 1 case was seen at this air field in the course of the present study. In this case the blepharitis was moderately severe and complicated with meibomitis. That the ocular manifestations were due in large part at least to infection with pathogenic staphylococci was indicated by the striking relief obtained from antistaphylococcic therapy. The importance of pathogenic staphylococci in blepharitis associated with rosacea has been stressed by Wise,[8] who found that none of the lesions of rosacea were influenced by riboflavin.

Pediculosis.—Pediculosis as a cause of blepharitis was considered in 2 cases of phthiriasis palpebrarum discovered at this air field; but in 1 case the presence of pubic lice and nits on the lashes did not lead to symptoms of blepharitis, and in the other blepharitis was present but cultures revealed pathogenic staphylococci. That the blepharitis was due to staphylococci rather than to the pediculosis was indicated by the fact that it persisted after the pediculi were eliminated. These observations were in accordance with my previous experience with phthiriasis palpebrarum in civilian life, in which the parasites produced minimal changes in the lid margin.

7. Thygeson, P., and Braley, A. E.: Local Therapy of Catarrhal Conjunctivitis with Sulfonamide Compounds, Arch. Ophth. **29**:760 (May) 1943.

8. Wise, G.: Ocular Rosacea, Am. J. Ophth. **26**:591 (June) 1943.

Trachoma.—Four cases of blepharitis were observed in patients with trachoma. In all 4 cases pathogenic staphylococci were recovered from the lid margins and were presumed to be causal. Blepharitis is not a manifestation of trachoma, as the virus does not attack the lid margins. It must, therefore, be considered a complication caused by superimposed infection with staphylococci or H. duplex.

INVOLVEMENT OF THE LIDS WITHOUT MARGINAL BLEPHARITIS

Numerous cases of allergic dermatitis of the eyelid were noted, but as the dermatitis involved the entire area of the lids and tended to spare the margins they were eliminated from consideration as cases of typical marginal blepharitis. No single case of true allergic involvement of the lid margins was observed. This is in sharp contradication to Lemoine,[9] who stated that allergy is a frequent cause of blepharitis.

A case of lichen planus with predominant involvement of the lids was seen, but the margins were spared.

As has already been noted, it seemed logical, in view of the high incidence of ringworm infection in troops stationed in Florida, to expect instances of infection of the lid margin with fungi of the ringworm group. A few such cases have been reported in the literature,[10] notably in children. At this air field no single case of marginal involvement was recognized, although 2 cases were seen with ringworm of the lid proper. These presented no diagnostic problem whatever.

IMPORTANCE OF MILD OR SUBCLINICAL BLEPHARITIS

Early in this study it became evident that blepharitis was a far more common disease than had generally been supposed. Routine examination of the lid margin with the slit lamp and corneal microscope in all cases of chronic conjunctivitis revealed a high incidence of inflammation of the lid margins which would have been missed if gross examination alone had been relied on. Biomicroscopically, however, differentiation between normal and pathologic lid margins could be made easily. Differentiation could also usually be made in this way between pure seborrheic and pure staphylococcic blepharitis, since the greasy scales of the seborrheic type look quite different microscopically from the dry, fibrinous flakes of the staphylococcic type. Many of these cases of biomicroscopic or subclinical blepharitis could be recognized

9. Lemoine, A. N.: Allergies in Ophthalmology, Arch. Ophth. **28**:79 (July) 1942.

10. Mata Lopez, P.: Arch. Soc. oftal. hispano-am. **2**:62 (Jan.-Feb.) 1943. Costa, O. G.: Microsporon Infection of Palpebral and Ciliary Regions, Arch. Dermat. & Syph. **48**:65 (July) 1943. Silvers, S. H.: Microsporon Audouini Infection of the Eyelashes, ibid. **49**:436 (June) 1944.

by examination with the ordinary loupe once attention had been called to them from study with the slit lamp.

In view of the well known causal relationship of blepharitis to conjunctivitis, it is clear that careful examination with the slit lamp of the lid margins in cases of chronic conjunctivitis should be made routinely. The conjunctiva could be treated indefinitely without result if the primary focus were in the lid margins and ignored. In my opinion, the importance of biomicroscopic examination in these cases cannot be stressed too highly.

SECONDARY ETIOLOGIC FACTORS IN BLEPHARITIS

Role of the Meibomian Glands.—In the majority of cases of blepharitis in this series involvement was limited entirely to the ciliary region of the lid margin, with complete sparing of the meibomian area. In these cases the meibomian glands showed no evidence of hypersecretion or of infection. Other cases were seen, however, in which, in addition to involvement of the ciliary area, the meibomian area showed hyperemia and maceration of the epithelium with dilatation of the meibomian orifices and hypersecretion and infection of the glands. It was in these cases that frequently recurring attacks of internal hordeolums and chalazions occurred. Smears from infected glands showed numerous leukocytes, with occasional scattered cocci and diphtheroid bacilli but no yeast forms or diplobacilli. The meibomitis was frequently spotty in character, perhaps only one or two glands on the entire lid margin being affected. It was noted that infection was rare in the absence of hypersecretion and that when it did occur it was in the form of internal hordeolums rather than of chronic meibomitis. In cases of chronic meibomitis atonic glands were found which had become converted into "pus pockets." A number of cases were seen in which isolated infected meibomian glands appeared to constitute foci for the continuance of the staphylococcic blepharitis.

Role of Vitamin Deficiency.—Recent studies [11] on vitamin B complex deficiency indicate that it may be a factor both in seborrheic dermatitis and in susceptibility to staphylococcic infection, and a deficiency of vitamin A has been suggested [12] as an etiologic factor in acne vulgaris, a disease shown to be related in some of its manifestations to blepharitis. For these reasons, the cases of blepharitis in this series were studied for clinical signs of vitamin deficiency, particularly Bitot's spots and prexerotic signs, extension of limbal capillaries,

11. Gross, P.: Non-Pellagrous Eruptions of the Skin Due to Deficiency of Vitamin B Complex, Arch. Dermat. & Syph. **43**:504 (March) 1941.

12. Saunders, T. S.: Favorable Effects of Vitamin A in a Case of Acne of Long Duration, Arch. Dermat. & Syph. **50**:199 (Sept.) 1944. Straumfjord, J. V.: Vitamin A: Its Effect on Acne, Northwest Med. **42**:219 (Aug.) 1943.

cheilosis and strawberry tongue. No clinical manifestations of vitamin A deficiency were noted, however, or any signs which could be attributed with any certainty to vitamin B complex deficiency. There was only 1 case of perlèche in the series. In this case the lesion was unilateral, contained pathogenic staphylococci and yielded to antiseptic therapy alone. In the only other case of perlèche observed no blepharitis or other ocular signs were present. In a considerable number of cases there was extension of limbal capillaries into the cornea, but the significance of this sign as evidence of riboflavin deficiency has been thrown into doubt by many observers.[13]

The patients were questioned as to their dietary habits, but in no case was there evidence of a grossly inadequate diet, past or present. This is in accordance with the findings of the officers of the medical service in this hospital, who have discovered no clinical cases of vitamin deficiency at this field and consider the Army diet maintained here to be adequate in vitamin A and vitamin B complex. As will be described later, the use of vitamin preparations did not noticeably affect the clinical course of blepharitis in 25 cases in which it was tried.

A number of patients reported excessive intake of fats or sweets or both, and some of these men were grossly overweight. Since excessive intake of fats could be a factor in the hypersecretion of the meibomian and sebaceous glands of the lid margin, and since excessive intake of sugar is known to increase susceptibility to staphylococcic infection, both excesses were curtailed in these patients. Such dietary improvement, however, resulted in no observable change in the blepharitis.

Role of Refractive Error.—Most textbooks mention the importance of correction of refractive errors in the treatment of blepharitis. Although it is somewhat difficult to see any direct connection between the two conditions, it is conceivable that eyestrain could result in congestion of the lid margins, with consequent hypersecretion of the meibomian glands and increased susceptibility to infection. As has also been claimed, refractive errors might possibly produce irritation of the lids, which would result in rubbing the lids with soiled fingers and thus lead to their infection. From the findings in 190 refractions, summarized in table 3, it seems unlikely, however, that refractive errors played any considerable part in the production of blepharitis in this series. It is of interest that the 2 patients with the most severe infection had 20/20 vision in each eye and showed only insignificant hyperopic errors on cycloplegic refraction. The patients receiving glasses for correction

13. Scarborough, H.: Circumcorneal Injection as a Sign of Riboflavin Deficiency in Man, Brit. M. J. **2**:601 (Nov. 21) 1942. Scott, J. G.: Corneal Vascularity as Sign of Ariboflavinosis, J. Roy. Army M. Corps **82**:133 (March) 1944. Sebrell, W. H.: Nutrition in Preventive Medicine, J. A. M. A. **123**:342 (Oct. 9) 1943.

of refractive errors were carefully questioned as to whether or not they felt that the wearing of the glasses alleviated their symptoms. While a few claimed that their eyes felt more comfortable with the glasses, the general opinion was that the disease had not been noticeably influenced.

Role of Personal Hygiene.—There was some evidence in this series to indicate that Army conditions, particularly in the heat and glare of Florida, caused exacerbations of blepharitis. There were a number of soldiers who stated that although the condition had been present since

TABLE 3.—*Refractive Errors in 190 Cases of Blepharitis* *

	Number of Cases
Emmetropia	44
Myopia	22
Low	3
Moderate	12
High	7
Hyperopia	15
Low	15
Moderate	0
High	0
Hyperopic astigmatism	12
Low	11
Moderate	0
High	1
Myopic astigmatism	5
Low	5
Moderate	0
High	0
Mixed astigmatism	13
Low	12
Moderate	1
High	0
Compound hyperopic astigmatism	42
Low	26
Moderate	12
High	4
Compound myopic astigmatism	36
Low	15
Moderate	16
High	5

* Low error means less than 1.00 D.; moderate error, 1.00 to 3.00 D.; high error, 3.00+ D.

childhood they had never had serious trouble with it until entering military life. The main factor seemed to be the difficulty of maintaining personal cleanliness under field conditions, which tended to increase staphylococcic infections of the skin generally.

Role of Allergy.—As previously noted, allergy appeared to play no etiologic role whatever in marginal blepharitis in this series, although there were a number of cases of allergic involvement of the entire lid area due to drug sensitivity and contact dermatitis caused by cosmetics. There were no cases in which the onset of the blepharitis could be ascribed to an allergic sensitivity, but it is certainly conceivable that a contact dermatitis might lead to secondary staphylococcic infection, which, in turn, might induce a staphylococcic blepharitis. No examples

of such a sequence were observed, however. Numerous cases of allergic conjunctivitis due to pollens were studied, but no single case of blepharitis was found among them. In 3 cases of vernal catarrh with secondary staphylococcic infection moderately severe staphylococcic blepharitis and meibomitis were present; but most vernal catarrh, as seen in civilian practice, is not accompanied with blepharitis, and it seems unlikely that the association of the two conditions in these 3 cases was other than accidental.

Role of Heredity.—There appears to be a definite hereditary factor in blepharitis. In a significant number of cases in this series there was a history of familial occurrence, particularly in parents and grandparents. This hereditary predisposition was stressed by Aubaret and was noted by me in previous studies on staphylococcic blepharitis. It is, of course, possible that communicability of the disease accounts for the familial occurrence, but its failure to spread from husband to wife, or vice versa, as was noted in this series, is indicative of a low degree of communicability. Just what the hereditary factors concerned consist in could not be ascertained in this study. The well known susceptibility of blond skins to blepharitis was observed, however, the disease being relatively rare among brunette and Negro troops.

Role of the Endocrine Glands.—The role of endocrine factors could not be determined in this series. The relationship of seborrhea to the endocrine glands is well recognized, however, and leaves small doubt that they play a part in many cases by contributing to the hyperactivity of the sebaceous and meibomian glands, which, in turn, increases the susceptibility of the lid margins to the development of blepharitis.

COMMENT

In view of the steady advances currently being made in specific therapy of infectious disease, it is increasingly important to determine the etiologic factors in ocular disease. The cause of many ocular infections is still unknown and many are not specific entities. It is evident from this and other studies that blepharitis is by no means an etiologic entity but has a varied etiology, comparable to that of other infections of mucocutaneous junctions, such as perlèche.[14] It is also suggested by this study that mixed infections are almost as common in blepharitis as pure infections.

In the absence of direct lid inoculation experiments with staphylococci, the pathogenic role of these organisms in blepharitis must be assumed on the basis of present knowledge of the staphylococcic dermatoses. It is well known that staphylococci have a special predilection

14. Finnerud, C. W.: Perlèche: Its Nosologic Status, J. A. M. A. **126**:737 (Nov. 18) 1944.

for the skin and attack this tissue in various ways to produce the clinical pictures, for example, of impetigo, infectious eczematoid dermatitis and folliculitis. These types of cutaneous reaction were seen in the cases of staphylococcic blepharitis of this series. Furthermore, the etiologic relation of staphylococci to certain types of blepharitis is clearly evident from therapeutic studies in which elimination of the organisms resulted in rapid healing of the disease and failure to do so resulted in its persistence.

It is difficult to make a clear distinction between pathogenic and nonpathogenic staphylococci in spite of the numerous studies which have been made on the subject. The criterion used in this series, i. e., the ability of the organism to give a positive reaction to the coagulase test, is certainly not 100 per cent reliable. On clinical grounds it is suspected that certain coagulase-negative strains of Staph. aureus are pathogenic for the lid margins, but further studies will be required to prove or disprove this suspicion.

In the interests of speculating on the origin of the infection of the lid margin, an attempt was made to obtain the history of onset in each case. While the data secured were not sufficiently reliable to warrant statistical analysis, certain information of value was obtained. Most patients with staphylococcic blepharitis gave a history of onset in childhood. Certain of these men recalled definite onset after measles, impetigo, acute conjunctivitis or hordeolum. In the few cases of recent onset the blepharitis usually followed an attack of sties or of acute conjunctivitis. It is well known that pathogenic staphylococci are found very commonly in the nose, particularly in the external nares. It is safe to assume that transfer of organisms from this reservoir to the eyelids by way of fingers or handkerchiefs frequently occurs.

The etiologic role of seborrheic dermatitis in blepharitis must be assessed on clinical grounds alone, since the cause of the cutaneous disease itself is still in dispute. The etiologic relation of the two conditions is clinically apparent, however, from the identity of the lesions of the lid margin with those of seborrheic dermatitis of the scalp and brow. It is probable that P. ovale will eventually be shown to be the etiologic agent. It was constantly present in the cases of seborrheic blepharitis of this series, and its demonstration in large numbers in scrapings from the lid margins is advanced as a diagnostic sign in spite of the fact that small numbers are occasionally found on the clinically normal lid. In this series the correlation between laboratory and clinical findings in cases of seborrheic blepharitis was found to be very close.

Blepharitis due to H. duplex, which has long been recognized as a disease entity, was surprisingly infrequent in this series considering the fact that it is known to occur commonly in various parts of the country. Diagnosis is not difficult, as the organisms are usually numer-

ous in scrapings from the lid margins and identifiable on morphologic grounds alone, so that cultural studies are unnecessary. In the 4 cases in this series the typical involvement of the angles was present; but in a few cases of pure staphylococcic origin this clinical feature was also displayed, so that diagnosis on strictly clinical grounds is not completely reliable. It is known that H. duplex is also frequently found in the nose, particularly in the external nares. It is likely, therefore, as has been presumed for staphylococcic blepharitis, that many cases of blepharitis due to this organism arise as a result of transfer of infectious material from the nose.

It is of interest that with but few exceptions a cause could be assigned to every case of blepharitis. This, of course, does not mean that determination of the etiologic agent was accurate in every case, but it does indicate the probability that the common causes of blepharitis are limited to a relatively few agents. In isolated cases, of course, a variety of agents not found in this series may well be the cause. It is believed, however, that this study clearly shows that the ordinary ringworm fungi are not commonly concerned in the disease, since ringworm was prevalent among the patients of this series and the tropical conditions of Florida were conducive to spread of the infection. In spite of this, not a single instance of infection of the lid margin was noted among these patients. It seems probable from this study that streptococci, particularly beta hemolytic streptococci, can occasionally produce or contribute to the production of blepharitis but that they do so rarely.

Demodex folliculorum, an acarus-like parasite often found in the sebaceous follicles of the face, has been suggested as a possible cause of blepharitis, but it was not recognized in scrapings from the lid margins or in expressed meibomian secretion in any case in this series.

There seems to be no doubt that increased activity of the sebaceous glands of the lid margins predisposes to blepharitis, particularly the seborrheic variety. However, there were a number of clearcut examples of staphylococcic infection of the lid margins in persons with normal skins.

This study has emphasized the importance of routine slit lamp study of the lid margins in all cases of chronic conjunctivitis. When cases of the mild, subclinical form thus uncovered are included, blepharitis, with its associated chronic conjunctivitis, becomes the most common external infection of the eye.

SUMMARY AND CONCLUSIONS

1. Blepharitis was the most common external infection of the eye seen in military personnel at this station. In addition to constituting a cosmetic blemish, it was an important cause of ocular disability, both in itself and as a source of conjunctivitis, keratitis and other complica-

tions, causing irritation, blurring of vision due to increased secretion, epiphora, photophobia and eyestrain.

2. Laboratory and clinical studies of a series of 350 cases indicated that only three important types of blepharitis occurred; namely, staphylococcic blepharitis, seborrheic blepharitis and Hemophilus duplex blepharitis. There were many cases of mixed staphylococcic and seborrheic infection. Other causes were unimportant.

3. The three main etiologic types of blepharitis had distinct clinical characteristics and in their pure forms could be differentiated on clinical grounds alone in all but a few cases in which staphylococcic blepharitis simulated H. duplex blepharitis.

4. Microscopic examination of scrapings from the lid margins facilitated determination of the etiologic agent. The finding of budding yeast forms, believed to be Pityrosporum ovale, was considered a diagnostic sign of seborrheic blepharitis, although its etiologic role in seborrheic dermatitis is still unsettled.

5. Routine biomicroscopic examination of the lid margin in cases of chronic conjunctivitis revealed a high incidence of mild or subclinical blepharitis, which was usually staphylococcic. It is suggested that most cases of chronic conjunctivitis have their origin in blepharitis, which in many instances will escape notice unless magnification is used.

6. Secondary factors in the causation of blepharitis were found to be, in order of their importance: (1) increased activity of the sebaceous and meibomian glands, (2) poor personal hygiene under field conditions of military life and (3) tropical climate, which predisposes to a high incidence of infectious dermatoses. There was no evidence to indicate that vitamin deficiency, refractive error or allergy played significant roles.

II. TREATMENT

A great number and variety of procedures have been advocated for the treatment of blepharitis. Aubaret,[1] in his extensive review, described more than fifty. In this study it was proposed to test and compare the commonly applied procedures and to evaluate them in relation to the etiology, as elucidated in section I. In addition, it was proposed to test the therapeutic efficiency of the new chemotherapeutic agents, particularly sulfathiazole and sulfadiazine, penicillin and tyrothricin. Owing to movements necessarily incident to military personnel, there was a great variation in the time during which treatment could be carried out. Two hundred and sixteen cases, however, were studied therapeutically over a sufficient period of time for conclusions to be drawn from the results.

As indicated in section I, only three important etiologic types of blepharitis were found in this series. These were seborrheic blepharitis,

staphylococcic blepharitis and blepharitis due to H. duplex. In addition, there was a large group of cases of mixed staphylococcic and seborrheic infection. The treatment of each of these four groups will be considered separately.

The Lid Margin as a Skin Structure.—Although blepharitis would seem to be fundamentally a dermatologic problem, there are certain characteristics of the skin of the lid margin which set it apart from the skin of other areas of the body and make it a special therapeutic problem. As is best observed with the slit lamp and corneal microscope, the lid margin is divided into two zones, an anterior zone, containing the cilia, and a posterior zone, containing the orifices of the glands of Zeis and Meibom. The two zones are separated by a fine gray line. The anterior zone, containing the cilia, is entirely cutaneous and can be compared with other hairy areas of the body, such as the brows or scalp; but the posterior zone forms a transitional area between skin and mucous membrane and differs from all similar transitional areas of the body in that it contains the orifices of the meibomian glands. These modified sebaceous glands, which are of unusual length, introduce a unique element into the problem of blepharitis because of their tendency to secretory derangement and their susceptibility to infection. Furthermore, the fact that the lashes are the only hairs on the body which, because of the irritating effect of soap on the eyes, do not participate in the ordinary soap cleansing of the face and scalp further differentiates the lid margins from other comparable structures and has a bearing on the treatment of blepharitis. The proximity of the conjunctiva and cornea, moreover, limits in many respects the type of therapeutic measure which can be employed, since many semi-irritant agents well tolerated by the skin are not at all tolerated by the mucous membranes.

Treatment of Seborrheic Blepharitis.—There were 52 cases in this series in which the diagnosis was pure seborrheic blepharitis. As previously described in the section on etiology, their most important characteristics were dull, dirty, generally greasy, nonadherent flakes or crusts on the lid margins, with hyperemia and infiltration of the underlying tissues. While a dry type of seborrheic blepharitis has been described and was seen in a few cases, the greasy scaling associated with hypersecretion of the sebaceous glands was present in the vast majority of cases in this series. The condition was never seen without seborrheic dermatitis of the scalp, which appeared in all cases to be the primary focus.

The usual dermatologic treatment of seborrheic dermatitis, as described in modern textbooks of dermatology, follows four main lines: 1. Dietetic treatment: Avoidance of alcohol and foods rich in fat, such as butter, peanut butter, pork products, salad oils and fried foods. 2. Endocrine treatment: Small doses of thyroid extract for overweight

patients with low basal metabolic rates. 3. Local treatment of cutaneous lesions: Chief reliance on resorcinol, sulfur, salicylic acid and the mercurial preparations, especially ammoniated mercury. 4. Local treatment of the scalp, as the probable primary source: Application of agents used on cutaneous lesions, often in combination, and shampoo at least twice a week.

An attempt was made to apply these dermatologic procedures to the treatment of seborrheic blepharitis. After considerable experimentation, the following routine was worked out: 1. Treatment of scalp infection and any other areas of seborrheic dermatitis. Most cases were referred to Capt. Morris Waisman, M.C., chief of the dermatologic section, but occasionally patients with the mild form were treated without consultation by means of biweekly shampoos with liniment of soft soap U. S. P. and biweekly applications of an ointment compounded as follows:

	Gm.
Ammoniated mercury	8.0
Salicylic acid	4.0
Cetyl alcohol base, to make	100.0

2. Local treatment of the lid margins: Manual expression of the meibomian glands; careful removal twice a week of scales, sebaceous material and desquamated epithelium by vigorous massage of the lid margins with cotton swabs moistened with solution of boric acid or 1 per cent silver nitrate; application of an ointment, consisting of 1 per cent salicylic acid and 1 per cent yellow mercuric oxide in a petrolatum base, with vigorous massage. For home use, the same ointment was prescribed to be used night and morning with gentle massage, the excess ointment to be left on at night but removed in the morning. If any symptoms of conjunctivitis were present, a collyrium of a 1:5,000 solution of mercuric oxycyanide was prescribed for use two or three times daily. 3. Investigation of dietary habits. An attempt was made to correct excesses or other dietary errors.

This therapeutic regimen proved to be very successful except for the definite tendency of the condition in many cases to recur. This was particularly true of the few cases in which overactivity of the meibomian glands was the most prominent feature. In most of these cases the condition recurred as soon as treatment was stopped. Recurrences could be minimized, however, by the use of the ointment once or twice a week over an indefinite period.

Other methods of treatment which were given a trial included applications to the lid margins two to four times daily of 2.5 per cent ammoniated mercury ointment, 1 per cent resorcinol ointment, 1 or 2 per cent sulfur ointment or 1 per cent sulfur combined with 1 per cent salicylic acid in an ointment base. Applications twice weekly of 3.5 per cent tincture of iodine were also tried. Acidolate, a water-soluble sul-

fonated oily detergent, was occasionally used for cleansing the lid margin but had the disadvantage of being somewhat irritating to the conjunctiva and cornea. Soaps were also tried for this purpose but proved to be impractical because of the impossibility of limiting their action to the lid margin. None of these procedures was found to have any appreciable advantage over the routine method previously outlined.

A few patients complained of slight irritation from the use of the salicylic acid–yellow mercuric oxide ointment, but in general it was well tolerated. Two cases of sensitivity to mercury were encountered and confirmed by means of patch tests. A typical contact dermatitis occurred, which was relieved by substitution of another medicament for the mercurial ointment.

Treatment of the scalp infection seemed to have a favorable effect on the control of the disease of the lid margins. Reinfection of the lid margins from an active scalp disease by means of the fingers must be considered a possible cause of recurrence.

A group of selected patients with seborrheic blepharitis were treated with the sulfonamide ointments (5 per cent sulfathiazole or 5 per cent sulfadiazine), penicillin ointment and tyrothricin ointment, without effect. Fifteen patients were given large doses of preparations of the vitamin B complex over periods varying from two to six weeks without local treatment of any kind; no obvious change in the infection of the lid margins was observed, and all 15 patients later showed satisfactory response to routine local therapy.

Attempts to improve dietary habits were not altogether satisfactory, owing to the lack of cooperation on the part of some patients and to the difficulty of adjusting diets under military conditions. Only a few patients lived at home, where they could effectively control their diets. In the few who maintained a low fat diet, it was impossible to demonstrate any material decrease in sebaceous activity or any appreciable change in the disease.

Treatment of Staphylococcic Blepharitis.—As described in the section on etiology, pure staphylococcic blepharitis was found to have clinical characteristics which differentiated it from the other two main etiologic types, seborrheic blepharitis and the form caused by H. duplex. The nonulcerative form was characterized by dry, adherent scales on an inflammatory base, and the ulcerative form, by pustules involving the superficial hair follicles and leading to the formation of shallow ulcers. Complications of hordeolum, meibomitis, conjunctivitis and keratitis were common. Of these, meibomitis was the most persistent and troublesome to deal with.

The therapeutic problem in staphylococcic blepharitis revolves on the following necessities: (1) to destroy the bacteria in the lesions; (2) to eliminate or treat predisposing causes, such as seborrhea, and

(3) to eliminate other staphylococcic infections of the skin, such as impetigo, folliculitis or furunculosis, which could serve to reinfect the lid margins. The main difficulty lies in the destruction of such staphylococci as have gained entrance to the glands of the lid margin, particularly the meibomian glands.

The following groups of therapeutic agents were tested in the 90 cases of staphylococcic blepharitis in this series: (1) antiseptics or germicidal agents not having specific antistaphylococcic action, including silver nitrate, yellow mercuric oxide, ammoniated mercury, mercury bichloride, mercuric oxycyanide, iodine, salicylic acid, merthiolate, zinc sulfate and Quinolor (a mixture of three chlorine derivatives of 8-hydroxyquinoline); (2) dyes, including gentian violet medicinal N. N. R. and brilliant green; (3) sulfonamide drugs, including sulfathiazole and sulfadiazine; (4) antibiotic substances, including penicillin and tyrothricin, and (5) vaccines, including staphylococcus toxoid and stock and autogenous vaccines.

Tests with Ordinary Antiseptic Drugs.—Application of silver nitrate in 1 or 2 per cent strength to the lid margins, and simultaneously in 0.25 per cent strength without neutralization to the conjunctiva, proved a useful procedure, especially in cases of recent origin. The blackening effect of silver nitrate was prevented by the fact that antiseptic ointments were also used routinely after each application.

After considerable experimentation, the following routine was found to give a satisfactory result in many cases: applications of silver nitrate as just detailed twice a week, combined with applications twice a day of the 1 per cent salicylic acid–1 per cent yellow mercuric oxide ointment to the lid margins, preceded by the instillation of drops of 1 : 5,000 solution of mercuric oxycyanide into the conjunctival sac. A 2.5 per cent ammoniated mercury ointment was used occasionally as a substitute but appeared to have no advantage over the yellow mercuric oxide–salicylic acid ointment.[14a] With this routine, improvement was obtained in the majority of cases and apparent cure in a considerable number. Other preparations tried included merthiolate (1 : 5,000) ointment, mercury bichloride (1 : 3,000) ointment; Quinolor ointment, and 1, 2 and 3.5 per cent tinctures of iodine. No noteworthy results were obtained with any of these preparations except tincture of iodine, which appeared to be very useful, especially in cases of the ulcerative type. It was impossible to use 3.5 per cent tincture of iodine in most cases continuously, however, owing to irritation of the lid margins, but weaker dilutions were well tolerated.

Test with Brilliant Green and Gentian Violet Medicinal.—A limited number of patients, selected because of failure to respond to other forms of therapy, were tested with these two dyes. Neither preparation could

14a. Various ointment bases were tested but petrolatum was found to be as satisfactory as any.

be employed routinely because of its disfiguring cosmetic effect, which most patients refused to tolerate. Improvement was obtained in the 4 patients treated with a 2 per cent alcoholic solution of gentian violet medicinal, but it was impossible to follow them long enough to be sure that permanent cures had been achieved.

The brilliant green was applied once daily in a 5 per cent alcoholic solution. It was important to avoid spreading the solution onto the conjunctiva, as it proved to be rather irritating. Fortunately, it was not irritating to the lid margin itself. Five patients to whose lids the dye was applied over periods ranging from two to five weeks were apparently cured but could not be followed long enough for the results to be conclusive. A case of exceptionally severe ulcerative blepharitis of long duration which had resisted all previous treatment is of particular interest. The history follows:

A. C., aged 25, had pure staphylococcic blepharitis, which had been present since childhood and was complicated by recurrent ulcerative lesions with loss of cilia and accompanied by moderately severe keratoconjunctivitis. Cultures revealed a hemolytic Staph. aureus, which was coagulase positive and fermented mannitol and was found to be resistant to both sulfathiazole and penicillin. Previous routine medication had failed, and treatment with sulfathiazole, penicillin, tyrothricin, staphylococcus toxoid, autogenous vaccine and roentgen radiation was ineffective. Over a two year period all methods of therapy proved entirely useless. Brilliant green applied to the lid margins daily produced immediate improvement. The pustules and ulcerations ceased forming immediately and have not recurred over a two month period of observation. Cilia began to reform, and at the time of the last examination only slight hyperemia of the lid margins remained. Cultures yielded no pathogens.

This and other experiences with brilliant green in this series suggest that it is of definite value in the treatment of staphylococcic blepharitis.

Tests with Sulfathiazole and Sulfadiazine.—These drugs were employed in 5 per cent concentrations in various bases, the commonest being a hydrous wool fat–petrolatum mixture. Vanishing cream bases and other varieties frequently employed on the skin proved to be too irritating for use around the eye. The preparations were used four times daily by preference but in many cases could be used only twice daily.

Both sulfathiazole and sulfadiazine appeared to be much more effective than ordinary antiseptics, and the majority of patients showed satisfactory improvement or healing. A much higher percentage of apparent cures was obtained when the disease was of recent onset than when it was of long duration. The clinical response was usually prompt; as a rule there was demonstrable improvement within four or five days if there was to be any at all. As will be described later, this was also true in penicillin therapy.

Early in the study it was noted that patients without meibomitis responded much more satisfactorily to local sulfonamide therapy than those with it. In the latter event it was necessary to institute supplementary therapy, consisting in manual expression of the glands combined with staphylococcus toxoid or vaccine or both. Although patients whose infection was of recent onset were always benefited by this treatment, patients with long-standing disease were frequently not relieved, even by repeated expressions of the meibomian glands over long periods. That meibomitis was probably the major cause of therapeutic failure in this series is evident from examination of table 4, which lists the results in 216 cases. On clinical grounds it became evident that local chemotherapy with the sulfonamide drugs or with penicillin, even in cases of known strain susceptibility, was not the answer to the problem. The reason for this failure in the case of penicillin therapy was shown experimentally in 2 cases to be due to failure of the drug to penetrate

TABLE 4.—*Results of Treatment in 216 Cases of Blepharitis* *

	Slight or No Improvement	Improvement	Healing
Seborrheic blepharitis	2	24	26
Staphylococcic blepharitis			
Without meibomitis	2	38	30
With meibomitis	6	13	1
Blepharitis due to Hemophilus duplex	0	0	4
Mixed seborrheic and staphylococcic blepharitis			
Without meibomitis	2	37	11
With meibomitis	3	16	1

* Treatment time at least three weeks.

the meibomian glands after it had been applied to the lid margin repeatedly. Nor could penicillin be demonstrated in expressed secretion from the meibomian glands in 2 cases in which a full therapeutic dose was given by the intramuscular route.

In 4 cases sensitization to sulfathiazole was observed during the course of treatment. In 2 of these cases there was a history of previous oral therapy with sulfathiazole which had been followed by cutaneous eruptions. No sensitivity to sulfadiazine was observed. In order to minimize the possibility of drug sensitization, the period of treatment for the sulfonamide drugs was limited to seven days.

The effect of oral sulfadiazine therapy on staphylococcic blepharitis was observed in 4 cases in which treatment was being given for infection of the respiratory tract. It is noteworthy that no permanent improvement occurred in any of them.

Tests with Penicillin and Tyrothricin.—Penicillin was employed in 87 cases. The routine method of application was in solution form (500 units per cubic centimeter) and as an ointment (1,000 units per gram

in a petrolatum or a petrolatum–hydrous wool fat base). The drops were instilled four times daily, and the ointment was applied night and morning. In certain test cases the ointment alone was used every hour during the waking hours. Penicillin sensitivity tests were performed on each culture (table 5), but the penicillin was employed irrespective of the results of the tests in order to obtain data as to their clinical value.

TABLE 5.—*Penicillin Sensitivity of 98 Strains of Pathogenic Staphylococci*

Strain Sensitivity, Oxford Units per Cc.	No. of Strains	Strain Sensitivity, Oxford Units per Cc.	No. of Strains
Inhibited by:		Inhibited by:	
0.005	1	0.32	5
0.01	2	1.0	5
0.02	16	5.0	1
0.04	23		
0.05	3	Not inhibited by:	
0.08	11	5.0	25
0.15	5	500.0	1

TABLE 6.—*Correlation of Penicillin Sensitivity and Clinical Response in 48 Cases of Staphylococcic Blepharitis*

Strain Sensitivity, Oxford Units per Cc.	No Improvement	Improvement	Healing
Inhibited by:			
0.01	1	..	..
0.02	1	6	1
0.04	2	8	2
0.05	1	1	..
0.08	..	2	5
0.16	..	1	..
0.32	..	1	..
Not inhibited by:			
5.0	14	1	..
500.0	1	..	..

TABLE 7.—*Clinical Response to Penicillin Therapy in 43 Cases of Staphylococcic Blepharitis* *

No Change	Improvement	Healing
6	24	13

* Penicillin sensitivity not known.

Penicillin proved to be moderately effective (tables 6 and 7) in relieving the symptoms of staphylococcic blepharitis, but the results still left something to be desired. In a few instances clinical cure without relapse was obtained in as short a time as a week; but in general relapses were frequent, and in some cases the condition proved completely resistant.

Two special bases were employed in an effort to obtain greater release of the penicillin into the tissues, but clinical results with these preparations were not noticeably better than with the others.

In 4 cases sensitivity to penicillin developed during therapy. Typical contact dermatitis developed, and positive reactions to patch tests were obtained. As will be seen in table 6, there was a definite correlation between penicillin sensitivity in vitro and clinical response to penicillin therapy. Response usually became apparent within forty-eight hours if it was to occur at all.

Tyrothricin was employed in only 14 cases, owing to the necessity of purchasing it privately. The cases were partially selected in that only those were used in which the disease had resisted ordinary methods of therapy. The drug was applied in the form of drops (33 mg. per hundred cubic centimeters) and ointment (50 mg. per hundred grams), exactly as in the case of penicillin. In 6 of the 14 cases there was pronounced improvement, but the condition in the rest was unchanged. In the concentrations employed the drug was not irritating to the conjunctiva or the lid margins. In view of the partial success obtained, it is believed that this method of treatment deserves further study.

Tests with Staphylococcus Toxoid and Vaccines.—Previous studies by Murray [15] and by me [16] indicated that staphylococcus toxoid was of value in the treatment of staphylococcic blepharitis which had resisted ordinary methods of treatment. This was denied in a report by Julianelle, Boots and Harrison [17] but was apparently confirmed in a series of studies by Allen.[18] Pathogenic staphylococci are known to elaborate exotoxins capable of producing severe inflammation when instilled into the conjunctival sac or injected into the skin. The rationale for the use of toxoid to induce antitoxic immunity is therefore clear. At the same time, it must be realized that pathogenic staphylococci also have endotoxins, which appear to be concerned with the organism's invasiveness. Their presence forms the rationale for the use of vaccines, either stock or autogenous.

In this series staphylococcic toxoid was administered in 55 cases, but in only 27 cases was the full course given. Only in cases of blepharitis which was complicated by meibomitis or by severe conjunctivitis or keratitis or in cases in which the condition had resisted routine treatment was toxoid therapy given. It was used as a supplementary measure only, local treatment being continued in every case. It was not possible in mixed therapy of this type to appraise the value of the toxoid injec-

15. Murray, D. S., and Glasg, M. B.: Staphylococcus Toxoid, Lancet **1**:303 (Feb. 9) 1935; cited by Julianelle, Boots and Harrison.[17]

16. Thygeson, P.: Treatment of Staphylococcic Blepharoconjunctivitis with Staphylococcus Toxoid, Arch. Ophth. **26**:430 (Sept.) 1941.

17. Julianelle, L. A.; Boots, R. H., and Harrison, G. H.: The Treatment of Staphylococcal Infections of the Eye by Immunization with Toxoid, Am. J. Ophth. **25**:431 (April) 1942.

18. Allen, J. H., in discussion on Thygeson.[16]

tions, but the general impression gained was that they were of distinct value. The few patients who showed extensive cutaneous reactions to intradermal injections of the toxoid improved more rapidly than those with minimal or negative cutaneous reactions.

Only 1 patient was treated with a staphylococcus toxoid combined with stock vaccine. This patient had a severe staphylococcic blepharitis, complicated with meibomitis, conjunctivitis and keratitis, which was totally resistant to local therapy, including applications of sulfathiazole ointment and penicillin. During a course of treatments with the toxoid the keratitis disappeared and the conjunctivitis improved, although pathogenic staphylococci persisted on the lid margin.

Stock vaccine was used in only 8 cases and autogenous vaccine in only 1. These vaccines were used in conjunction with staphylococcus toxoid in all 9 cases, so that, although the blepharitis improved in 8 cases during and after therapy, it was impossible to evaluate the results.

Treatment of Blepharitis Due to H. Duplex.—In the 4 cases of uncomplicated blepharitis due to H. duplex in this series healing was rapid after short periods of treatment with sulfathiazole ointment used four times daily. No recurrences were noted. The classic treatment with zinc sulfate in the form of drops and ointment has been equally effective in cases I have seen in the civilian population unless there was mixed infection with staphylococci.

Treatment of Mixed Seborrheic and Staphylococcic Blepharitis.—Cases of this common type of blepharitis presented the most difficult therapeutic problem of the series. The results obtained in treatment were definitely inferior to those obtained with either the pure seborrheic or the pure staphylococcic disease.

After considerable experimentation, it was found that the seborrheic factor was best treated first. This was done by the same methods as those employed in treating pure seborrheic blepharitis, particular attention being given to the meibomian glands, which were expressed frequently. The most satisfactory local treatment appeared to be applications of the 1 per cent yellow mercuric oxide–1 per cent salicylic acid ointment. Again, scrapings from the lid margin were used as a guide to therapy. After the slides became negative for P. ovale, a course of treatments with sulfathiazole or penicillin ointment was prescribed, and when meibomitis was present staphylococcus toxoid was employed. Under this regimen, satisfactory clinical improvement was obtained in most cases and clinical cures in a moderate percentage.

Other treatments employed, including use of tincture of iodine, sulfur and resorcinol, offered no appreciable advantages.

The importance of keeping the scalp and other areas of the skin free from active seborrheic dermatitis was evident in numerous cases

in this group in which involvement of the lid margins recurred repeatedly until infection of the scalp was controlled.

Treatment of Secondary Conjunctivitis and Keratitis.—In cases of pure seborrheic blepharitis, conjunctivitis was an infrequent complication and was readily controlled by the use of mild antiseptics, such as 0.25 per cent silver nitrate combined with a collyrium of a 1 : 5,000 solution of mercuric oxycyanide, used two or three times daily. There were no corneal complications.

In cases of pure staphylococcic blepharitis, conjunctivitis and keratitis were serious complications. The conjunctivitis varied from a mild catarrhal type to a severe form with copious mucopurulent exudate and intense cellular infiltration of the membrane. The corneal complications also varied from superficial epithelial keratitis with punctate erosions, staining with fluorescein, located most prominently in the lower portions of the cornea, to fulminating keratitis with multiple corneal infiltrations and ulcers. In all these cases it was obvious that treatment of the lid margins was of first importance and conjunctival treatment of secondary importance. In none of the cases of corneal involvement was it necessary to treat the cornea directly by chemical or actual cautery. All methods of antistaphylococcic treatment described for blepharitis were effective in these cases, but sulfathiazole and penicillin were superior to the ordinary antiseptics. The use of staphylococcus toxoid was particularly valuable in the treatment of the corneal complications, especially the superficial keratitis with punctate epithelial erosions.

In cases of mixed seborrheic and staphylococcic blepharitis the conjunctivitis and keratitis were also serious complications but differed in no important way, except in resistance to treatment, from the complications occurring with pure staphylococcic blepharitis. In all types of staphylococcic conjunctivitis and keratitis the primary role of the infection of the lid margin was obvious.

As is always true, conjunctivitis due to H. duplex accompanied the blepharitis caused by the same organism in the cases in this series and responded well to sulfathiazole ointment. It has been seen to respond equally well to zinc sulfate in cases in the civilian population.

COMMENT

The treatment of blepharitis, other than the type due to H. duplex, which is no problem, cannot be said to be wholly satisfactory at present. Although the majority of patients can be relieved under ideal conditions, there is one inescapable factor which militates against permanent cure; treatment with present methods is at best a long-drawn-out affair, and even at a military post, where cure is free and the time lost in reporting to the clinic is at government expense, certain patients will not cooperate for the required length of time. Under civilian conditions failure to

complete the course occurs much more frequently. It is clear that future control of the disease will depend largely on the development of measures which will be effective in days or weeks, rather than in months. The recent advances in chemotherapy appear to offer only a partial solution to the problem.

From this study it is apparent that infection of the meibomian glands is the greatest single factor which must be overcome. Meibomitis was present in all cases in which the blepharitis was resistant to therapy, and methods of treating it were obviously inadequate. Repeated expression of the glands was a useful procedure and in some instances resulted in apparent cure. In general, however, expression was only palliative. The inability of both general and topical chemotherapy with the sulfonamide drugs and with penicillin to affect the condition was also made clear in this series. In the case of penicillin at least, it was shown experimentally that the drug failed to enter the secretions of the meibomian glands in demonstrable amounts after local and intramuscular therapy, and the finding was confirmed clinically by the fact that penicillin-sensitive organisms were cultured from these secretions during the course of both types of treatment. In this connection, it is of interest to report a case of internal hordeolum which developed in a patient receiving 100,000 units of penicillin daily. The strain of staphylococcus recovered from the hordeolum was fully sensitive to penicillin. Hypersecretion of the meibomian glands, with dilatation of their orifices, appeared to be the main factor in their susceptibility to infection. No satisfactory means of reducing this hypersecretion is at present known. In selected cases in this series reduction of fats in the diet had no noticeable effect on it.

In view of the minimal clinical symptoms incident to pure seborrheic blepharitis, it is apparent that its principal importance lies in its role of providing a suitable soil for the growth of pathogenic staphylococci. The chief problem is the matter of recurrence. The importance of treating the primary focus, the scalp, which is stressed in all textbooks of dermatology, was amply confirmed in this study, for, although it was impossible to say positively that recurrences were due to reinfection, the general impression was gained that reinfection from the scalp was common.

Assuming that P. ovale is the cause of the disease, the fungicidal effect of all the agents used in this series, including tincture of iodine, silver nitrate, salicylic acid, ammoniated mercury and yellow mercuric oxide, was evident from examination of scrapings from the lid margins, which were negative for the yeast after treatment. The failure of penicillin or of sulfathiazole to influence the condition is in accordance with the known fact that these drugs fail to affect mycotic infections.

The recent dermatologic literature has been full of reports [19] criticizing topical applications of the sulfonamide drugs because of the high incidence of allergic reactions. The danger of sensitization has appeared to outweigh the benefit to be obtained from local therapy. The results in this series, however, would seem to indicate that sulfathiazole and sulfadiazine can be used for topical application around the eyes with minimal danger, since only 4 cases of sensitization occurred in the group of over 300 patients treated; in 2 of the 4 cases, moreover, sensitization was clearly related to previous oral use of the drug. No sensitivity to sulfadiazine developed in any of the 60 cases in which it was employed. Long-continued use of the sulfonamide drugs in treatment of blepharitis, however, would seem to be not only unwise but unnecessary, for if there is to be any clinical response to the drug it will occur within fifteen days, at the longest.

Sensitization to penicillin (or possibly to impurities contained in it) occurred in 5 cases in a considerably smaller series, and in my opinion was of more significance than the allergic reactions to sulfathiazole. There is no adequate substitute for penicillin at the present time, so that sensitization could be a serious matter in the event that general penicillin therapy was later needed. On the other hand, since cross sensitization among the sulfonamide compounds is not common, sensitivity to sulfathiazole does not necessarily preclude all subsequent sulfonamide therapy. For this reason, it is recommended that topical use of penicillin be reserved for those cases in which the disease has failed to respond to other medication and that its administration be limited to not more than ten days.

In this series the only instances of "overtreatment dermatitis" observed were 3 cases in which daily applications of 3.5 per cent iodine were used. The condition was readily recognized and treatment discontinued. The possibility of the deleterious effect of overtreatment was considered at all times, and frequent rest periods, as well as rotation of procedures, were employed in cases of long-drawn-out treatment for the purpose of detecting it.

Several cases of severe keratitis accompanying blepharitis appeared to be related to insufficient closure of the lids while sleeping. It was possible to obtain observations on the patients during sleep and to show that they did not have normal closure of the lids. Other patients with blepharitis, however, had the same symptom but no keratitis. It is probable, therefore, that the keratitis was primarily staphylococcic in origin and was aggravated, rather than caused, by the drying effect of incomplete closure of the lids.

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19. Cole, H. N.: The Local Use of Sulfonamide Compounds in Dermatology, J. A. M. A. **123**:411 (Oct. 16) 1943.

In this series patients with well established blepharitis in general exhibited a genuine desire to be cured and were extraordinarily faithful in reporting to the clinic for treatment. Careful questioning, however, revealed that they were not so faithful in the daily use of their medications. As their conditions improved, they became more and more careless about treating themselves. The relative efficacy of clinic versus home treatment was well illustrated in a series of 15 consecutive patients who were available for daily treatment. Improvement was much more striking than in patients who could be treated only once or twice a week.

SUMMARY AND CONCLUSIONS

A large series of cases of blepharitis among military personnel were subjected to therapeutic study with the following five groups of medicaments: (1) antiseptic or germicidal drugs, including silver nitrate, zinc sulfate, yellow mercuric oxide, ammoniated mercury, mercuric oxycyanide, mercury bichloride, tincture of iodine, salicylic acid, sulfur, resorcinol, Quinolor and merthiolate; (2) dyes, including gentian violet medicinal N. N. R. and brilliant green; (3) sulfonamide drugs, including sulfathiazole and sulfadiazine; (4) antibiotic substances, including penicillin and tryothricin, and (5) vaccines, including staphylococcus toxoid, toxoid combined with vaccine and stock and autogenous vaccines.

Seborrheic blepharitis responded best to the following treatment: (1) daily mechanical cleansing of the lid margins; (2) frequent expression of the meibomian glands; (3) applications of 0.25 per cent solution of silver nitrate to the conjunctiva and 1 per cent silver nitrate to the lid margins twice weekly; (4) applications twice daily of an ointment containing 1 per cent yellow mercuric oxide and 1 per cent salicylic acid to the lid margins, and (5) treatment of associated seborrheic dermatitis of the scalp, brows and external ears. Sulfathiazole and penicillin applied in ointment form were ineffective.

Staphylococcic blepharitis responded well to topical treatment with the following preparations, listed in order of efficacy; penicillin; sulfathiazole or sulfadiazine, and mercurial preparations, including ammoniated mercury ointment and a combination of 1 per cent yellow mercuric oxide and 1 per cent salicylic acid in a petrolatum base. Administration of staphylococcus toxoid proved to be an important supplementary procedure. Other measures of therapeutic value included topical application of tincture of iodine, gentian violet medicinal and brilliant green to the lid margins. Treatment of other staphylococcic infections of the face or scalp was important.

In cases of staphylococcic blepharitis a close correlation between the sensitivity of the strain of staphylococcus to penicillin and the clinical response of the disease to topical penicillin therapy was noted.

Staphylococcic blepharitis complicated by meibomitis was much more resistant to therapy than uncomplicated blepharitis.

Blepharitis due to Hemophilus duplex, of which 4 cases occurred, responded completely and rapidly to topical application of sulfathiazole in ointment form.

Mixed seborrheic and staphylococcic blepharitis proved to be more resistant to therapy than either form alone. It was found best to treat the seborrheic factor first and to give particular attention to expression of the meibomian glands. After scrapings from the lid margins had become negative for P. ovale, antistaphylococcic treatment with sulfathiazole or penicillin ointment was employed. Staphylococcus toxoid was a valuable supplementary treatment.

Contact dermatitis as a result of allergy to both penicillin and sulfathiazole was observed but did not occur often enough to prejudice their use.

In pure seborrheic blepharitis, conjunctivitis was an infrequent complication and was readily controlled by the use of mild antiseptics; there were no corneal complications. In pure and mixed staphylococcic blepharitis, conjunctivitis and keratitis were serious complications, requiring conjunctival treatment with antistaphylococcic agents. The importance of the infection of the lid margins as the primary focus was obvious in all cases.

While local chemotherapy with the sulfonamide drugs and with penicillin constitutes a great advance in the treatment of staphylococcic blepharitis, the results in this series indicate that therapy is still not entirely satisfactory, especially in cases complicated with meibomitis.

Adequate treatment of blepharitis is of distinct military importance both for the removal of local irritation and for the prevention of serious corneal complications.

Major Alfred M. Glazer, M.C., chief of the laboratory service, placed all laboratory facilities at my disposal, and Capt. Joseph S. Gots, S.C., bacteriologist, and his technicians made the culture studies. Capt. Morris Waisman, M.C., chief of the section of dermatology, served as dermatologic consultant, and my associates, Major S. R. Irvine, M.C., and Capt. Joseph W. Hallett, M.C. aided in the clinical study.

524 Sainte Claire Building, San Jose, Calif.

RETROBULBAR NEURITIS AND COMPLETE HEART BLOCK CAUSED BY DIGITALIS POISONING

Report of a Case

HENRY P. WAGENER, M.D.

H. L. SMITH, M.D.

AND

ROBERT W. NICKESON, M.D.

Fellow in Ophthalmology, Mayo Foundation

ROCHESTER, MINN.

ALTHOUGH disturbances of vision resulting from digitalis intoxication have been described in many forms and by many investigators, no definite instance of retrobulbar neuritis caused by digitalis poisoning appears to have been reported in the literature. Recently, Carroll [1] reported 6 cases of colored vision caused by digitalis intoxication. No defects in the visual fields were present in these cases. In a discussion of his own paper,[2] he mentioned that Dr. D. F. Gillette, of Syracuse, N. Y., had observed 2 cases of retrobulbar neuritis resulting from digitalis poisoning. These cases, as yet, have not been reported in the literature.

Colored vision is a rather common visual manifestation of digitalis poisoning. The chromatopsia is most common for yellow or green, but red, brown, blue or white vision has been described.[3] Langdon and

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From the Section on Ophthalmology (Dr. Wagener) and the Section on Medicine (Dr. Smith), the Mayo Clinic.

1. Carroll, F. D.: Visual Symptoms Caused by Digitalis, Am. J. Ophth. **28**: 373-376 (April) 1945.

2. Carroll, F. D., in discussion on Carroll, F. D.: Visual Symptoms Caused by Digitalis, Arch. Ophth. **34**:166 (Aug.) 1945.

3. (*a*) Carroll.[1] (*b*) Chamberlain, E. C.: Digitalis Poisoning, J. Florida M. A. **28**:586-588 (June) 1942. (*c*) Giesler, F., and Wolff, K.: Beitrag zur Xanthopsie nach Digitalis, Klin. Monatsbl. f. Augenh. **79**:203-208 (Sept. 2) 1927. (*d*) Langdon, H. M., and Mulberger, R. D.: Visual Disturbance After Ingestion of Digitalis, Am. J. Ophth. **28**:639-640 (June) 1945. (*e*) Robey, W. H.: Visual Disturbances with Digitalis Medication, New England J. Med. **213**:248-251 (Aug. 8) 1935. (*f*) Smith, H. L. J.: Digitalis Delirium with Colored Vision: Report of One Case, J. Iowa M. Soc. **21**:173-174 (April) 1931. (*g*) Sprague, H. B.; White, P. D., and Kellogg, J. F.: Disturbances of Vision Due to Digitalis, J. A. M. A. **85**:716-719 (Sept. 5) 1925. (*h*) Willius, F. A.: Cardiac Clinics; Digitalis Poisoning with Cerebral Symptoms; Coronary Sclerosis with Angina Pectoris, and Paroxysmal Dyspnea, Proc. Staff Meet., Mayo Clin. **10**:649-653 (Oct. 9) 1935.

Mulberger [3d] stated that a relative central scotoma was present in case 4 of their series, but they intimated later that a marked change in refraction accounted for the blurring of vision. In several reports frosted or snowy vision has been noted.[4] Flickering sensations before the eyes also have been described, first by Purkinje, who used himself as a test subject and recorded the toxic manifestations.[5] "A peculiar oscillating movement of the eyes" was described by Galentine [6] in the case of an 8 or 9 year old boy, who recovered completely in a few days after withdrawal of the digitalis. Blurring of vision has been noted many times, and 1 case of temporary complete blindness was reported in the literature [7]; but in few cases has the visual acuity been recorded and the visual fields plotted. Some authors [8] have specifically made note of the absence of defects in the visual fields, but the rest either were unable to make perimetric studies or neglected to report the absence of field defects.

Carroll [1] postulated:

> . . . the confused vision is due to central functional impairment which, in turn, is due to the drug. . . . The temporary complete blindness mentioned in the literature probably was due to the cerebral intoxication; that is, a cortical type of blindness was induced which disappeared on stopping the drug.

This conception, namely, a central intoxication, has been generally accepted as the cause of the visual disturbances associated with digitalis poisoning. The purpose of this paper is to demonstrate that digitalis poisoning can affect not only the higher cerebral centers but also the papillomacular fibers of the optic nerve. Digitalis has a selective action on the vagus nerves, the auriculoventricular conduction mechanism and

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4. Carroll.[1] Langdon and Mulberger.[3d]

5. Hanzlik, P. J.: Jan Evangelista Purkyné (Purkinje) on Disturbances of the Vision by Digitalis, One Hundred Years Ago, J. A. M. A. **84**:2024-2025 (June 27) 1925.

6. Galentine, C. B.: Cumulative Effects of Digitalis, Boston M. & S. J. **49**: 205-206, 1854.

7. (*a*) Langdon and Mulberger.[3d] (*b*) Sprague, White and Kellogg.[3g] (*c*) Adams, P., in discussion on Gunn, J. A.: Toxic Amblyopia, Tr. Ophth. Soc. U. Kingdom **50**:396, 1930. (*d*) Berger, E. H.: Digitalis Intoxication, Northwest Med. **32**:195-196 (May) 1933. (*e*) Carr, J. G.: Digitalis Delirium, M. Clin. North America **9**:1391-1398 (March) 1926. (*f*) Edward, J.: On a Case of Poisoning by the Root of Digitalis Purpurea, Lancet **2**:31-32 (July 14) 1849. (*g*) Jackson, H., Jr., and Zerfas, L. G.: A Case of Yellow Vision Associated with Digitalis Poisoning, Boston M. & S. J. **192**:890-893 (May 7) 1925. (*h*) Parson, G. W.: The Visual and Cerebral Manifestations of Digitalis Intoxication: Case Report, Tri-State M. J. **7**:1375-1376 (Nov.) 1934.

8. Carroll.[1] Giesler and Wolff.[3c] Adams.[7c]

the sinoauricular node.[9] Hence, it is not incorrect to postulate the possibility of direct damage to the optic nerves secondary to generalized systemic intoxication. Weiss,[10] in discussing the effects of digitalis on the central nervous system, concluded that the yellow vision, which is frequently encountered, is due to disturbance of centers in the medulla and the midbrain, similar to the primary disturbance in function of the vagus nerve, which is the desired effect of the drug. Giesler and Wolff [3e] concluded that damage to the retrobulbar portion of the optic nerve caused the xanthopsia in their case, but they also mentioned the possibility of changes occurring in the refracting media, such as those seen with jaundice, and of cortical damage. In their case examination of the perimetric fields did not disclose any central defects but revealed loss of ability to recognize blue targets throughout the field.

Since digitalis is in constant and universal use today, and will continue to be used, its toxic manifestations cannot be overemphasized. Berger [7d] and Edward [7f] have both reported cases of fatal digitalis poisoning; hence, knowledge of its early toxic effects is of extreme value. It is significant to note that in the case reported by Giesler and Wolff the offending drug was not digitalis leaf, but gitalin, one of its glucosides.[3e] Smith [11] said that older persons, particularly those having arteriosclerosis, do not tolerate digitalis as well as younger patients and must be more closely observed for, and questioned about, the onset of toxic manifestations.

REPORT OF CASE

A white man aged 50 registered at the Mayo Clinic on April 2, 1945 because of poor vision, generalized weakness, nausea and vomiting. Two or three months previously he had had extrasystoles and had been given "leaf medicine," 1 tablet, four times daily for about two weeks. After two weeks his medicine had been changed to another "green digitalis tablet"; he had taken 1 tablet three times daily for six weeks. About two weeks before he came to the clinic his appetite had become poor; he had vomited several times and had had diarrhea, which had alternated with constipation. At the same time he had noticed that lights had become yellow and that green grass had assumed a yellow tint. His vision had also become blurred, and he had found himself unable to read. His local oculist had been unable to determine the cause of the blurred vision and, on finding blurring of the margins of the optic disks, suggesting increased intracranial pressure, had advised the patient to seek further advice.

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9. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 505.

10. Weiss, S.: The Effects of the Digitalis Bodies on the Nervous System: An Analysis of the Mechanism of Cardiac Slowing, Nausea, and Vomiting, Psychosis, and Visual Disturbance Following Digitalis Therapy, M. Clin. North America **15**:963-982 (Jan.) 1932.

11. Smith, H. L.: Cerebral Manifestations of Digitalis Intoxication, Proc. Staff Meet., Mayo Clin. **13**:574-575 (Sept. 7) 1938.

The blood pressure was 138 mm. of mercury systolic and 78 mm. diastolic. The pulse rate was 60 beats per minute, and the rhythm was regular. The heart was normal in size, and no significant murmurs were present. The abdomen was essentially normal except for bilateral inguinal hernia, for which the patient wore a truss. The prostate gland was moderately enlarged. The central nervous system was normal.

Corrected vision was 6/60 and 14/178 in the right eye and 6/60 and 14/224 in the left eye. Externally the eyes were normal. There was no imbalance of the ocular muscles, and the peripheral visual fields were full when tested by the confrontation method. The ocular fundi were essentially normal. The optic disks were flat; there were some thickening of the scleral rings and slight astigmatic blurring of the outlines of the disks. A few hyaline spots were present in the macular choroid of each eye. No gross vascular lesions were seen in the fundi. The central visual fields were plotted on the tangent screen at a distance of 1 meter (fig. 1). The field of each eye contained an 8 degree relative central

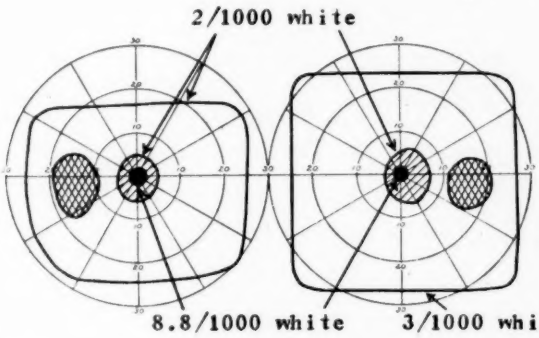


Fig 1.—Central scotoma in the field of each eye, taken April 2, 1945 with a tangent screen at a distance of 1 meter, showing density to a 8.8 mm. white target. The blindspots are slightly enlarged. Vision was 6/60 and 14/224 in the left eye and 6/60 and 14/178 in the right eye, with correction.

scotoma for a 2 mm. white bead. A small central focus in each scotoma was dense to an 8.8 mm. white target and to a red test object of the same size. Blue was not recognized in any part of either field. The physiologic blindspots were slightly larger than normal.

An electrocardiogram made on April 3, 1945 (fig. 2 *A*) revealed: a rate of 58; intermittent delayed auriculoventricular conduction and complete heart block; left axis deviation; slurring of the QRS complex in leads I and II; diphasic T waves in leads I and III and inversion of the T waves in lead III and diphasic T waves and depression of the S-T segments in the two precordial leads (CR_2 and CR_5). A flocculation test for syphilis gave negative results. The value for the hemoglobin was 11.7 Gm. per hundred cubic centimeters of blood; the erythrocyte count was 5,050,000, and the leukocyte count 14,600, per cubic millimeter of blood. Routine urinalysis did not reveal any abnormality. Roentgenologic examination of the thorax disclosed a Ghon complex on the left side. Roentgenograms of the head revealed calcification of the falx cerebri and slight hyperostosis of the right frontal bone.

The diagnosis was digitalis intoxication with complete heart block and toxic amblyopia due to retrobulbar optic neuritis. The administration of digitalis was discontinued, and increasing amounts of fluids were administered orally. The patient remained at the clinic for one week. During this time he was observed several times; the central visual fields were examined, and electrocardiograms were made. The visual acuity improved gradually; on April 9 the vision was 6/12 and 14/21 in the right eye and 6/10 and 14/21 in the left eye, with a + 2.00 D. lens added for near vision.

On the tangent screen at a distance of 1 meter there was in the field of each eye an 8 degree residual central scotoma for a 1 mm. white target. Within each central scotoma there was a small temporal paracentral scotoma, dense to a 3 mm. white target in the right eye and to a 2 mm. white target in the left eye.

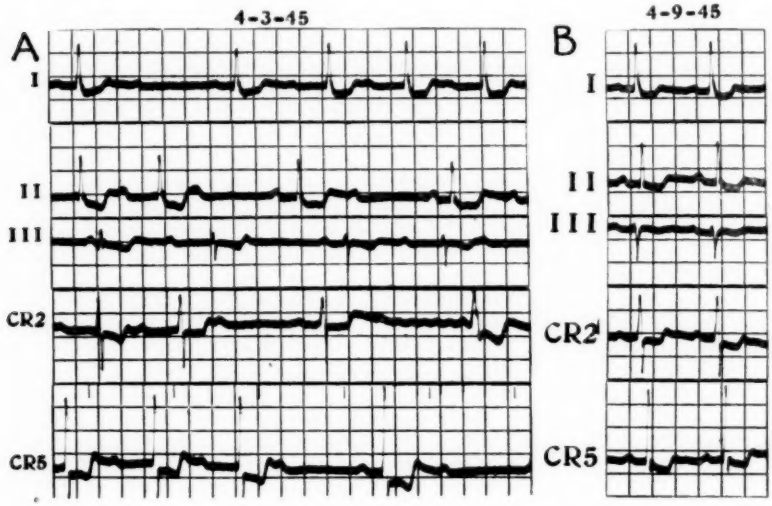


Fig. 2.—*A*, electrocardiogram made April 3, 1945, showing a rate of 58; intermittent delayed auriculoventricular conduction and complete heart block; left axis deviation; slurring of the QRS complex in leads I and II; diphasic T waves in leads I and III and inversion of the T waves in lead III, and diphasic T waves and depression of the S-T segments in the two precordial leads (CR_2 and CR_5).

B, electrocardiogram made April 9, 1945, showing a rate of 90; sinus tachycardia; slurring of the QRS complex in leads I and III; left axis deviation; diphasic T waves in leads I and II and inversion of the T waves in lead III, and diphasic T waves and slight depression of the S-T segments in the two precordial leads (CR_2 and CR_5).

An electrocardiogram made on April 9, 1945 (fig. 2 *B*) showed a rate of 90; sinus tachycardia; slurring of the QRS complex in leads I and III; left axis deviation; diphasic T waves in leads I and II and inversion of the T waves in lead III, and diphasic T waves and slight depression of the S-T segments in the two precordial leads (CR_2 and CR_5).

One month after his dismissal from the clinic, the patient reported by letter that his eyes and general physical condition had returned to normal.

COMMENT

In most cases of digitalis intoxication with disturbances of color vision the patients are hospitalized and are too ill to permit mapping of the perimetric and the tangent screen fields. Often, disorientation prevents even the gross determination of the visual acuity. When this can be determined with the use of bedside reading charts, it often is found to be considerably reduced; and when the fields appear to be normal with the gross confrontation test, the presence of central scotomas may be logically suspected. In the present case, it was fortunate that the patient's physical and mental condition was sufficiently good to permit the definite demonstration of bilateral central scotomatous defects in the fields of vision, although it was not possible to make complete perimetric studies. The vision returned to normal in about five weeks without treatment except for withdrawal of the digitalis and increasing the amount of fluid ingested by mouth.

The Mayo Clinic.

EXPOSURE AND FIXATION OF THE EYE IN THE EARLY DAYS OF CATARACT EXTRACTION

BURTON CHANCE, M.D.
PHILADELPHIA

OPHTHALMOLOGY, which might be likened to a highly specialized organ in the "body medical," has been characterized by an unfailing tendency to absorb into itself with imperious force whatever good might come within its grasp, while rejecting from its constitution all empiric elements which might have affected its vitality and, so to speak, metabolically, hindered the development of a creature which has, in time, influenced all medicine and led to the happiness of the world. It should be profitable for us as ophthalmologists, in this fiftieth century since the earlier recordings, to remind ourselves that this development has been but slowly progressive and that the hidden forces within the body were derived usually from single inventions or observations.

Today the tyro is inclined to accept the present status as he finds it, oblivious of how laboriously the science has struggled to attain its so great, stature. He accepts as matters of course many conditions now existing, and the practice of numerous technical procedures, just as though they had existed from the most primitive times, unaware of their obscure and halting beginnings.

Although I have been in practice many years, the extraction of cataract is as thrilling to me today as when I saw the operation for the first time. Constantly, my mind goes back to that event and asks, "What was the beginning of cataract operations like?" And, as I have observed the ease with which my young assistants have approached their vital cases, employing but few, simple instruments, I am reminded that once upon a time those instruments had not yet been devised to take the place of earlier, complicated and cumbrous implements.

Much has been changed in my own time. I recall my beginnings at Wills Hospital. One of my duties was the selection and preparation of instruments in time for the surgeons' visits in the afternoons. For one surgeon, the racks in each of the small metal trays should hold thirteen; for another, seventeen. Certain operators wished to have duplicates, handy to meet any emergency; yet, commonly, the most skilful might use only seven!

Read at the Eighty-First Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., Nov. 11, 1945.

Several years ago, while I was perusing Baron Wenzel's "Treatise on Cataract,"[1] as translated from the French, in 1791, my eye caught this sentence: "It is most extraordinary that amongst the eminent persons who have described the operation of extracting the cataract most of them have enumerated amongst its principal difficulties the quick and convulsive action of the eye, and that they should have taken such pains to contrive instruments for the purpose of fixing it." And, "There are some who still employ Specula, to fix the eye, notwithstanding the mischievous effects these always produce." And, again, "Why, from mere love of innovation, are new instruments continually introduced, which fall short of the boasted advantages attributed to them by their inventors?" "These admonitions," the Baron declares, he advances "only to describe and justify the teachings of his father," that famous peripatetic oculist who had gone about the Continent couching cataracts, on rich and poor, with great and variable success.

Having performed many extractions myself, I have witnessed uncounted numbers by the hands of "eminent persons," who but rarely enumerated, among the principal difficulties, the "quick and convulsive motion of the eye," although all had constantly "fixed the eyes" with instruments contrived for that purpose.

In the light of achievements and facilities, my thoughts run back to remoter times, causing me to wonder how old time surgeons exposed the globe to enable them to view the operative field and how they fixed the globe in order to prevent "convulsive motion."

Treacher Collins, while recounting incidents during his early days at Moorfields, told me that one of the surgeons, whose technic was the wonder of every visitor who came to the hospital, would allow the nails of the thumb and forefinger of his left hand to grow to an inch or more in length. With these "natural instruments" he could separate the eyelids and, at the same time, make gentle but firm pressure on the globe so that it was steadied and fixed, allowing him to make incisions and other motions with his right hand.

Such ruminations as these had led me to inquire into the history of the instruments and other appliances invented to simplify cataract extraction, with the development of surgical procedures which have done so much to allay the terrors which in former times seized the heart of the distressed subject at the prospect of so vital an operation.

One may now ask what the Baron, at the end of the eighteenth century, had to say on how to avoid the "Inutility and Inconveniences of Specula," his "long experiences having taught him that these instruments are always unnecessary, that a dexterous person may easily seize a moment in which the eye is motionless." He stated his belief that "so

1. Wenzel, J.: Treatise on the Cataract, translated from the French by J. Ware, London, C. Dilly, 1791, sec. 12, p. 78.

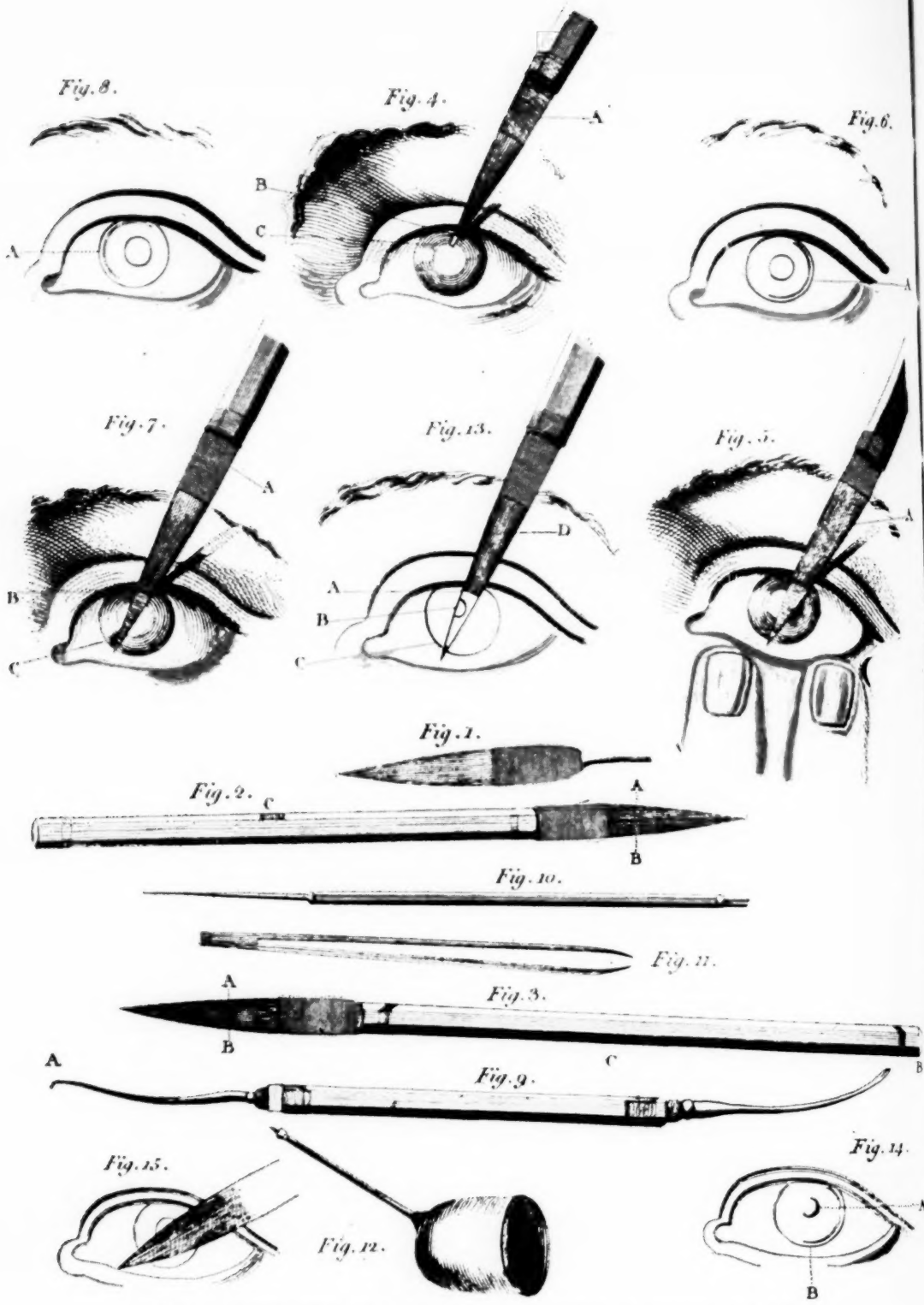


Fig. 1.—Above, drawings showing Wenzel's method of exposure and fixation of the globe, as well as incision with his special cataract knife; below Rumpelt's "silver thimble with its sharp attachment."

many different instruments not only render the operation more complicated but also are very liable to irritate and wound the eye," and, as he further declared, "they have been relinquished by the inventors themselves."

Wenzel could steady the globe while maintaining the perforation of the cornea with his cataract knife! He guardedly endorsed Rumpelt's "thimble with a sharp point attachment," devised by Fellen in 1782. This thimble was placed on the middle finger of the operator's left hand so as to impinge on the globe and in no way obstruct the use of his forefinger as it kept down the lower lid. Wenzel stated "that operators were often embarrassed by the wounding of the iris; that accident, [he felt] depended on the use of such instruments rather than on their being the means of preventing it."

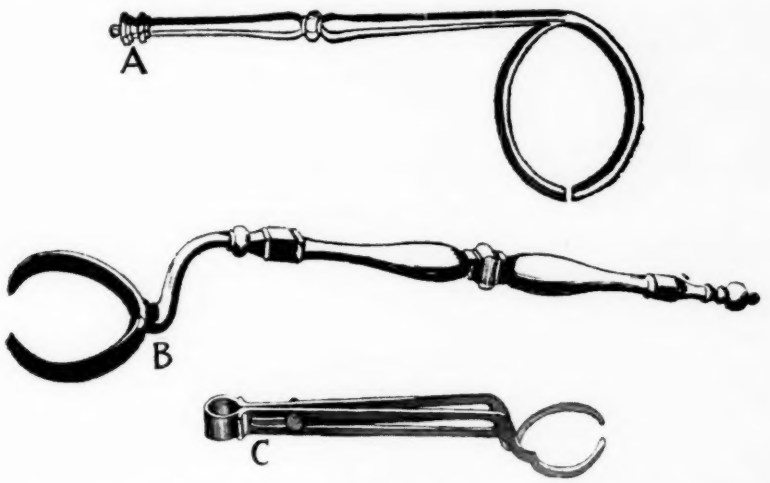


Fig. 2.—*A*, speculum devised by Paré (Paré, A.: Dix livres de la chirurgie, avec le magasin des instruments nécessaires à icelle, Paris, J. le Royer, 1564) to dilate and hold the lids steady; it can be enlarged and reduced according to the size of the eye. *B*, ocular speculum to keep the eye open (Fabricius ab Aquapendente, H.: Opera chirurgica, 1666). *C*, Cheselden's speculum, (Cheselden, W.: The Anatomy of the Human Body, ed. 4, London, W. Bowyer, 1730).

Certainly, in those days, fingers were trained to perform dexterously many duties. The Wenzels, father and son, looked on speculums as inconvenient and complicating, rendering the operation intricate and stated that "in the hands of an unskilled operator by slight pressure [this instrument] would rupture the capsule of the vitreous humors"; and the Baron could easily believe that the point of Rumpelt's instrument did "irritate and lacerate the membrane to which it was applied." In discussing the use of instruments, he insisted, that "the fewer instruments employed the less the eye is fatigued and, the more simple

the mode of performing the operation, the more certain will always be its success."

Ware, in commenting on Wenzel's disuse of instruments, and in the main agreeing with him, stated from his own extensive experience, especially in operations on congenital cataracts, that he had found it necessary to employ an elliptic ring with a handle attached with which, by gentle pressure on the ring, he forced back the lids and fully exposed and steadied the globe.

At this juncture it might be well to ask, "Which were the instruments the use of which Wenzel so strongly deprecated?" Had he seen the ellipsoid ring fixed rigidly in a rodlike handle, in use by Ambrose Paré in the middle of the sixteenth century? Or the cumbersome device of Fabricius ab Aquapendente, in the early 1600's? Or the somewhat similar one, more or less adjustable, devised by Cheselden, in his busy career in the eighteenth century? All these required the constant attendant care of an assistant; all of them were likely to "render the operation more complicated, embarrassing the operator besides being more dreadful to the patient." The Baron refers to several other instruments in use in his days; but I must forbear from an enumeration of their inventors in this brief essay.

A silk thread inserted through each side of the cornea, carried in a needle with the eye at its point, especially devised by M. Poyet,[2] he held to be useless for steadying the globe, because "that effect could be obtained by the cataract lancet"!

One may imagine some of the problems confronting the operator of those olden days. In attempting the incision, without some means of fixation, it was hardly possible for the surgeon to select the points of puncture and counterpuncture. The first contact of any sharp instrument was usually followed by jerking movements of the eyeball. The operator became impressed, inevitably, by the fact that the eyeball could not properly be steadied with the fingers. He was directed to wait until all muscular spasm had subsided before completing the section of the cornea. Fixation, with the lancet engaged, was especially dangerous because of the muscular contraction and general irritation from pressure on the globe. Many of the failures recorded were due to loss of vitreous through rupture of the hyaloid membrane. In time it became apparent that in order to expose the eyeball, instruments had to be invented with which to hold back the eyelids.

In the Museum of the College of Physicians, Philadelphia there is a great variety of long-forgotten instruments, many suggesting that fingers could not be excluded entirely, yet indicating that there are things that fingers cannot do. The most dexterous operator cannot sufficiently hold back the lid without exerting pressure on the ball.

2. Poyet, cited by Wenzel, J.: Mém. Acad. de chir. **2**:253, 1753.

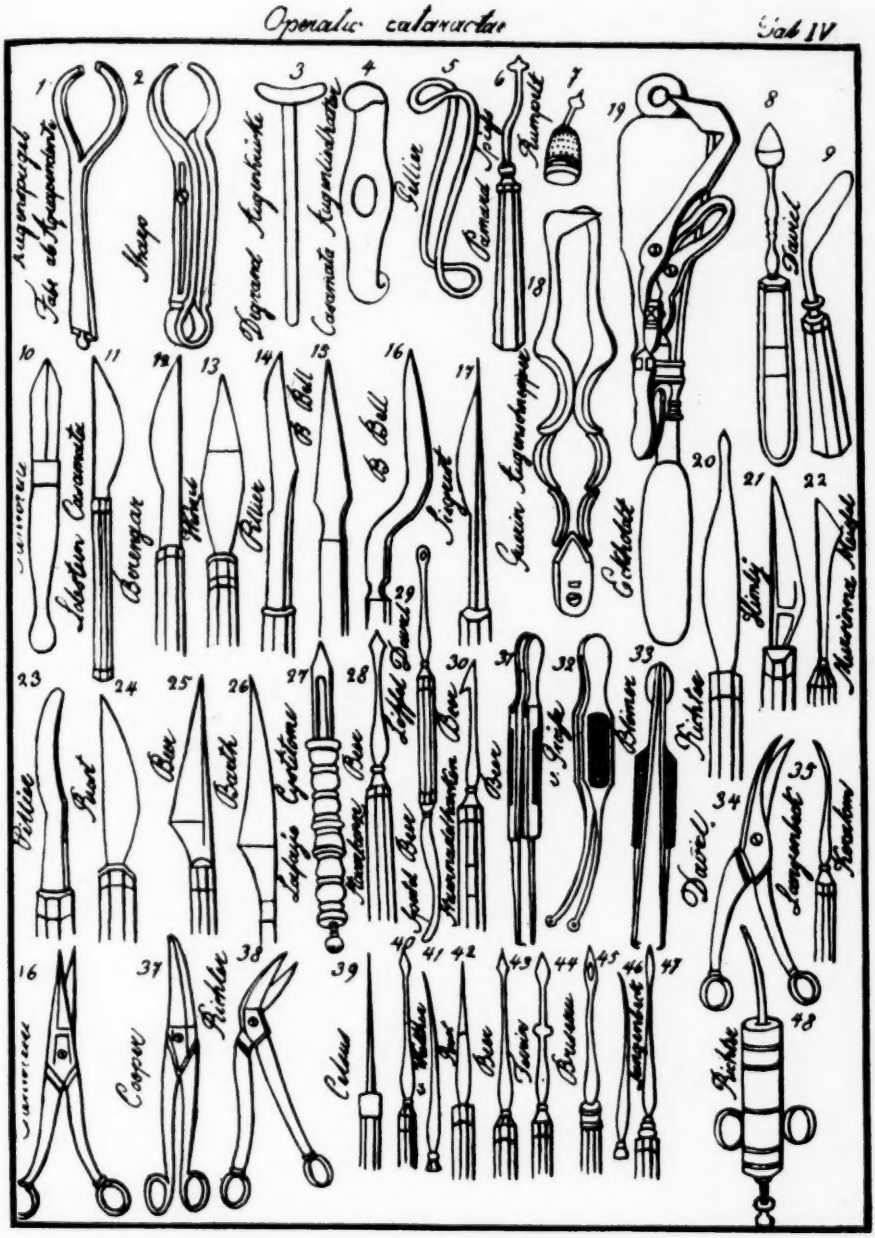


Fig. 3.—Instruments used in cataract operations (from Fritze, H. E.: Miniatur-Armamentarium, Berlin, A. Hirschwald, 1843).

It would seem that the Baron had not employed Pellier's "loop," devised about the middle of the eighteenth century, which consisted of a continuous thin silver wire with ends folded over, broad and hooklike,

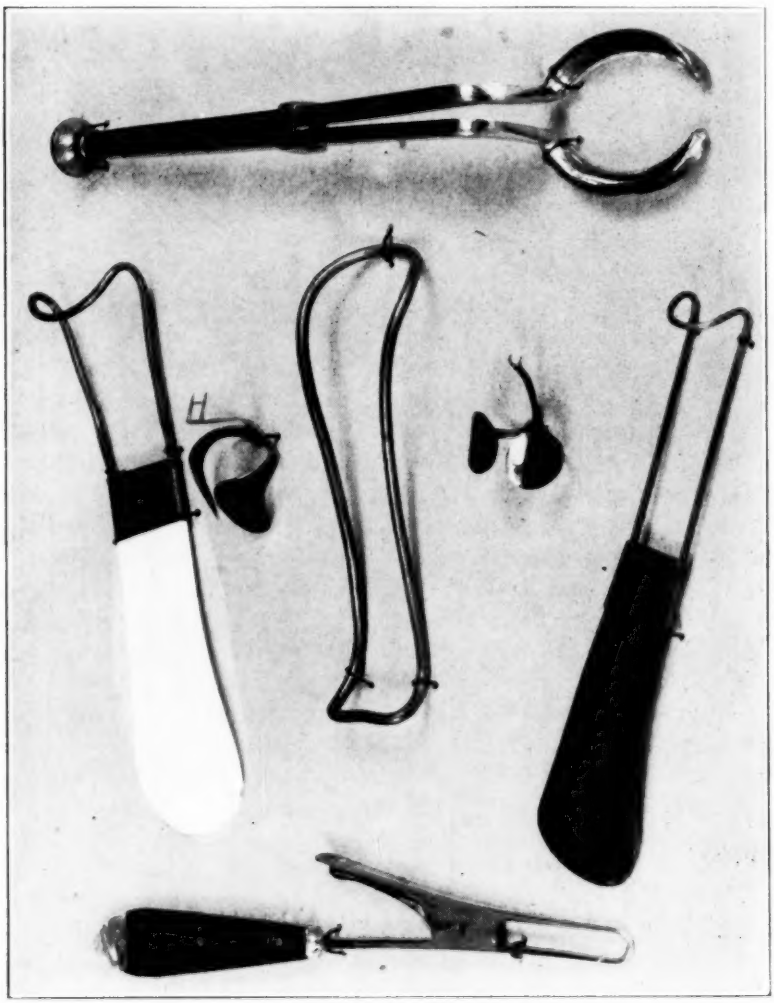


Fig. 4.—Display of antique instruments from the Museum of the College of Physicians, Philadelphia (by special permission), showing a Cheselden speculum, a Pellier lid elevator and two modifications, of later devising, of Rumpelt's *Fingerhut mit Stahlspiess.* Forceps (about 1850), inventor unknown.

for insertion under the upper lid; this served to withdraw the lid from the globe, the operator having only to manipulate the lower lid and steady the globe.

In the early years of the nineteenth century, Saunders,[3] the founder of Moorfields, noted that he, in performing the operation on children, had adopted other methods of combating the "excessive mobility of the eye in the unsteadiness of the little patient." This he overcame by fixing the eyeball with Pellier's "elevator" (fig. 5 *A*).

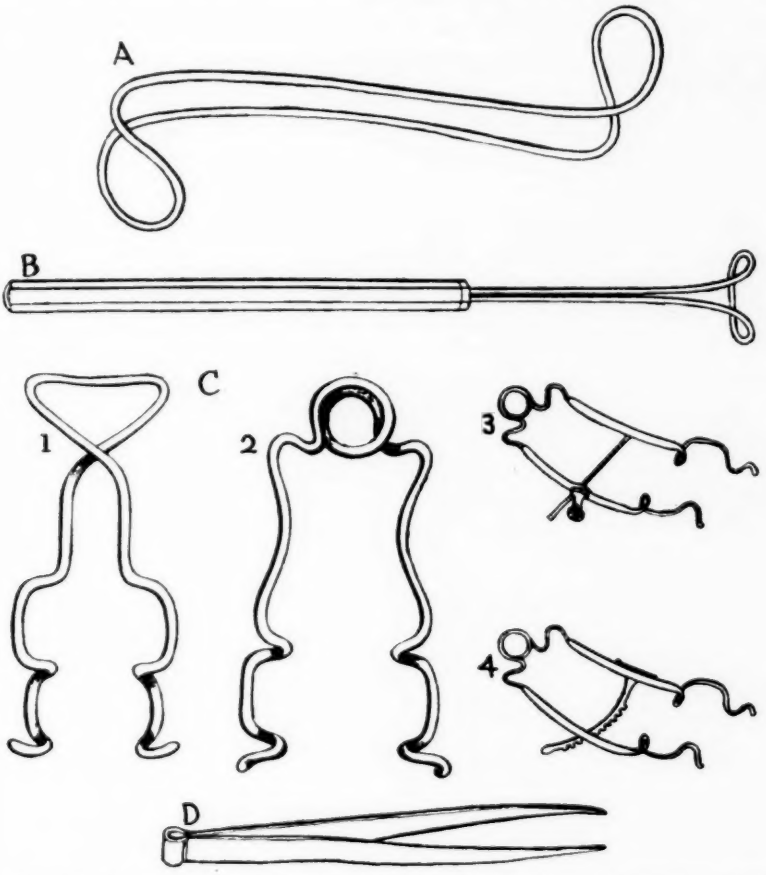


Fig. 5.—*A*, Pellier's eyelid elevator; *B*, Mackenzie's lid elevator (1854); *C*, early forms of speculums (*1*, Critchett, 1855; *2*, Bitterich, 1858; *3*, Bader, and, *4*, Bowman, 1864); *D*, an eighteenth century forceps.

. . . [He] required four or five assistants to confine the patient. The first fixed his head with reversed hands, the second not only depressed the lower lid with his forefinger but also received the chin of the child as in a crutch. The third confined the upper extremities and body, the fourth—the lower extremities. The surgeon seated behind the patient took the Pellier elevator in one or the other hand, according to the eye, and the needle in the right or left.[3]

3. Saunders, J. C.: A Treatise on Some Practical Points Relating to the Diseases of the Eye, London, Longman [and others], 1811, p. 117.

The surgeon gently introduced the bore of the speculum under the upper eyelid, his assistant depressing the lower lid, and at the moment that he was about to pierce the cornea he "fixed the eye by resting the speculum with moderate pressure on the eyeball." Saunders emphasized that "by consent which can only exist between the hands of the same person, using the speculum merely as an elevator of the lid, he [the surgeon] can not only discontinue the pressure, [but] with facility renew or regulate the pressure at the moment in which it may be required."

As Mackenzie,[4] at the end of the first quarter of the nineteenth century, commented: " . . . the want of exposure on the part of the patient may in an instant defeat the most perfect dexterity of the operator." It should be of interest to read the details of his instructions to the two or more assistants as to the means of exposing the eye and maintaining its composure. He himself steadied the eye by firm, yet the gentlest, pressure on the globe with his fingers. There is no hint as to the use of an anesthetic. "The fugitive eye is fixed without pressure by the fingers of an assistant and the operator. To whatever side it turned it met with the point of a finger except towards the temple, where the knife is about to enter." Then, he declared, "Various sorts of specula, spikes and hooks have been invented for fixing the eye; but all of them, except the silver wire, commonly called Pellier's speculum, are now discarded." He occasionally employed it, especially in operations on children, for supporting the upper lid, either applying it to the outer surface or introducing it beneath the edge of the lid. There was no better mode, however, of fixing the eye than by desiring the patient to look at the operator, who seized that moment for entering the instrument into the eye!

Such a "lid raiser" (fig. 5 *B*) served Mackenzie until about 1850, when he modified it by fixing into an instrument handle a rod, the end of which was a loop bent like the Pellier hook. This "elevator" was the prototype of the form now available in every instrument set.

During the same period it became necessary to adopt a fixing instrument, to afford the operator a firm grasp of the globe without lacerating or perforating a fold of the conjunctival tissues. At first the old form of dissecting forceps was employed, but that instrument was clumsy and ineffectual. Von Graefe, with his accustomed technical and artistic inventiveness, overcame those defects by devising one of delicate limbs wih teeth, two or more interlocking in the ends, which at once overcame the defects of the old forms. Somewhat later, some one devised a wire spring speculum, the "bows" of which could be inserted under both the upper and the lower lid and which was so adjustable as

4. Mackenzie, W.: A Practical Treatise on Diseases of the Eye, London, Longman [and others], 1830.

to be used without an assistant's aid. George Critchett, about 1855, and Wharton Jones, a few years later, employed this principle in forms which they used, but they found that the pressure of the spring could not be relied on. Bader and Bowman soon overcame this defect in pressure by affixing to the arms, spread to the desired width, a bar, secured with a screw or ratchet (fig. 5 *C*).

Inevitably, it was forced on operators that an appliance should be devised with which to separate and hold back the eyelids. It was deemed necessary that such an instrument should be self retaining, not likely to slip, stiff enough when in place to resist the action of a strong orbicularis muscle and capable of ready insertion and removal; it should exert no pressure on the globe, should be capable of adjustment to any desired width of opening and should never be in the way of an operator.

In the collection at the College of Physicians, Philadelphia, are a modified Cheselden speculum, a primitive Pellier elevator and several modifications of it, as well as the modified Rumpelt thimble spike. That spike was modified by Pamard, of Avignon, about 1840, by inserting it into an ordinary ivory handle. The Pellier loop was modified by cutting one end free and inserting the arms of the remaining portion into an ivory, tonguelike handle, which might be used in plastic operations on the eyelids. There are also several rather crude spring speculums.

One may dwell for a moment on the story of how later discoveries solved the problem of the means of controlling the patient and the field of operation.

Baron Wenzel did not deem it necessary to do much in the way of preparation prior to the operation. He could rely on the steadfastness of the patients to control themselves and the reliability of his assistants in their cooperation with him. When the sedative properties of the bromides and of chloral hydrate became known, these substances were given in fairly large doses in the preceding twenty-four hours. Preparations of opium and morphine were administered sparingly.

The discovery of the anesthetic powers of ether and chloroform proved a great boon to ophthalmic surgery. No longer must the surgeon adopt a speedy technic, necessitated by the struggles and distress of the patient, not seldom to the great disadvantage of the latter. Moreover, the employment of an anesthetic led promptly to modification of all operative procedures on the eye, as it had in general surgery. In seeking to obviate the instability of the globe, surgeons found that such anesthetics not only quieted the patient but, by overcoming the tendency to contract the rectus and orbicular muscles, had the additional advantage of facilitating the exposure and fixation of the eyeball.

Ophthalmic surgeons resisted employing chloroform for a long time on account of the vomiting which usually accompanied its use; they feared it might produce expulsion of the vitreous and hemorrhage within the globe. Furthermore, retching and vomiting hindered the operation, although the extraction might safely be completed after quiet was obtained. Moreover, there arose the question whether anesthetics should be used. The decision was determined by the courage of the patient! It was well known that many persons were capable of so great a degree of self control that the surgeon was enabled to perform the complete operation without an anesthetic!

When ether was first employed by the general surgeon, unpleasant effects were so frequent that Simpson suggested that chloroform might be substituted; and, in accordance with his dictum, it was used for many years. Yet chloroform occasionally caused death. The ophthalmic surgeon, therefore, hesitated to use the one or the other, and employment of an anesthetic became a serious matter on which he had to decide.

As already stated, anesthetics were rarely used in Europe, even as late as 1890, and surgeons, including some in America, avoided them except with nervous patients. Following the old custom of obtaining quiet and composure, the night before the operation they administered full doses of sodium bromide and chloral hydrate and repeated the doses an hour before operating. Morphine was sometimes given; yet opium was not always well borne. With children chloroform was used. Ether was employed for adults; yet for a speedy effect chloroform was given also.

In the late sixties and early seventies, as the administration of ether became more generally understood, it was found to be increasingly effective and safe, so that a steady return to its use was approved. In America, New England surgeons became increasingly adept in the administration of ether, and its quieting effects were seen to be sufficiently profound to favor the complete extraction of a cataract in a few brief minutes; their results influenced operators in England and on the Continent to use it.

Ether was employed by my distinguished teachers in most cases as late as the time of my own entrance into medicine. I assisted as the anesthetist many times, with satisfactory results; yet I was always directed "not to leave the hospital until assured the patients had fully recovered and their eyes were not uncomfortable." Dr. Norris repeatedly called attention to the fatal results he had known to follow the use of ether in patients with nephritis.

Many cumbersome and unwieldy contrivances were constructed with which to administer the fluid during the operation; none ever equaled a napkin, on which the ether was sparingly poured while the cloth was held over the face; by that simple means I have secured

complete relaxation and insensibility, in three or four minutes, having used less than 2 ounces (60 cc.) of ether.

Cocaine became of incalculable value because of its power to produce anesthesia by paralyzing the sensory nerves. Although this physiologic action had been generally known for years, it was not until 1884 that our own lately deceased fellow, Carl Koller, demonstrated in Vienna the practical value of cocaine in ophthalmic surgery. That discovery proved to be the final measure leading to surgical success and prevention

Fig. 6.—*A*, scene from Bartisch's "Augendienst"; *B*, a medieval method of controlling the patient during operation for cataract (Bartisch, G.: Augendienst, Leyden, 1522).

of the pain which operation had hitherto caused, in addition to its diminishing the great dread manifested by the sufferers. No longer were the surgeons' efforts frustrated by the constitutional effects produced by ether and chloroform anesthesia.

In times gone by, all the details of the cataract operation must have produced a formidable spectacle. Antique pictures tell one much. They show the patient fully dressed, as though he had just come in from the street and expected to return home. Or he might be seated in a chair,

his feet, legs, arms and hands lashed to the chair, his head held by an assistant, while the surgeon sat before him on a chair somewhat higher than the patient's. Years later, a number of assistants were usually employed. To take the place of an assistant, Laurence, in England, constructed a head clamp to be affixed to the operative bed. About 1850, the patient reclined or lay in bed, if not on a table, or, as there used to be at the Wills Hospital, a lounge! The patient walked into and

Fig. 7.—Photograph by Himly and Ruete, from Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, W. Engelmann, 1911, vol. 14, p. 2.

departed from the operation room in that revered hospital, and as late as 1912 I witnessed such an incident at a famous institution in Europe.

In conclusion, let me describe two scenes, in striking contrast to each other. The first is a detail from Joseph Warner's account, as detailed by Chandler.[5] Warner, a contemporary of Wenzel, was surgeon at Guy's Hospital.

5. Chandler, G.: Treatise on Diseases of the Eye, and Their Remedies, London, T. Cadell, 1780.

An assistant stands behind the patient, who puts his right hand under the patient's chin, after having covered the right eye, supposing it to be the left which is to be operated upon; the assistant then places the back part of the patient's head on his breast, at the same time directing the face upwards, to prevent the sudden discharge of the vitreous humor. He afterwards lifts up the superior eyelid with two or more of his fingers, taking care not to press upon the globe of the eye above; the operator at the same time depresses the inferior eyelid, with this precaution, not to press upon the inferior part of the globe of the eye till the incision is made. The patient must look straightforwards, and a little upwards. The operator now fixes his right elbow upon his right knee; after having put his right foot firmly on the patient's seat for this purpose. He then suddenly and resolutely introduces the point of his knife through the external part of the cornea.[5]

Today, a patient, having been admitted to the hospital after all studies have been made as to his general condition of health, and with the eye and adnexa free of possible infectious matter, is quieted with barbital and other sedatives and is placed in bed during the twenty-four hours prior to his entrance into the operation room. Then, after administration of cocaine or similar local anesthetic, perhaps by injection into the orbit, the speculum is adjusted, with exposure of the globe, which is then seized with delicate forceps and steadied so that the incision can be made and the extraction pursued—all without pain or discomfort. The patient may perhaps ask at the termination of the procedure when the surgeon will begin the operation, so that he might aid him in every way possible.

No longer could the Baron have declared that "pain attending cataract extraction is unavoidable," if, recently, he could have stood at the bedside with my house surgeon, to whom was given the care of an exceedingly timorous aged lady. No longer might he have dwelt on "the great difficulty under which the operator who employs instruments for the fixing of the eye labors from the want of a free, unconfined and unembarrassed use of both hands."

317 South Fifteenth Street.

Obituaries

GRADY EDWARD CLAY, M.D.
1889-1946

Grady Edward Clay, only child of Augustus C. Clay and Elizabeth Chupp, was born Aug. 12, 1889, in the village of Walnut Grove, Walton County, Ga. During his last illness he retired to the plantation where had lived five successive generations of his family, and died on July 11, 1946.

Dr. Clay obtained his primary education in the county schools and, at nearby Oxford, Ga., he graduated in 1910 from Emory College. He received his medical degree from the University of Michigan in 1914, and for the next three years he was resident physician in the department of ophthalmology, under the tutelage of Dr. Walter R. Parker. He returned to Georgia in 1917 to practice his specialty in Atlanta, but soon entered the Army in World War I. After serving as ophthalmologist in a base hospital in France, he was discharged in 1919 with the rank of captain.

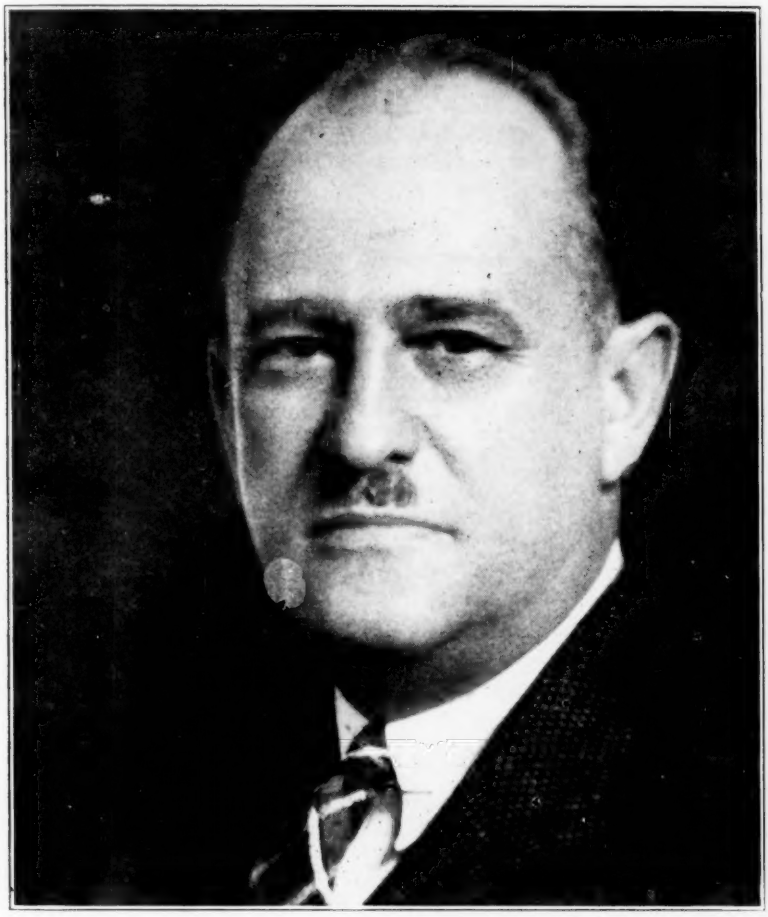
On resumption of his practice, Dr. Clay became associated with the department of ophthalmology of the Emory University School of Medicine. His ability and interest in teaching attracted notice, and his promotions were rapid. In 1939 he was made chief of the department of ophthalmology and in 1943 full professor. With the financial aid given the department in recent years by his influential friends and patients, special facilities for teaching and investigation became available, and a laboratory for ocular pathology and bacteriology was established.

In his lectures to the undergraduate students Dr. Clay was positive and straightforward, which characteristics made him an excellent teacher. Most instructive, to students and staff alike, were his ophthalmoscopy rounds of patients in the medical and obstetric wards of the city hospital. His great interest in medical ophthalmology, especially the vascular changes in the retina, was reflected in the widespread use of the ophthalmoscope by the students and by the members of the departments of obstetrics and of internal medicine.

Dr. Clay was an indefatigable worker, and because of his large private practice his hours were long. His private hospital work was done at Emory University Hospital; and there, through his efforts, many reforms were established for the more efficient handling of patients with ocular disease. In this hospital, on Tuesday afternoons, he held

his operative clinics, which were always varied and were frequently attended by visitors. He was an advocate of the round pupil intracapsular extraction of cataract, and his technic and skill were superlative.

Dr. Clay's contributions to ophthalmologic literature were not numerous, but an analysis of his major articles will show originality, careful preparation and a wide experience of the subject. He wrote especially



GRADY EDWARD CLAY, M.D.
1889-1946

on the subject of angioid streaks, and his number of personally collected cases was almost 70. He also contributed much to the knowledge and understanding of the changes in the retinal vessels associated with cardiovascular-renal disease. The subject had fascinated him for

twenty-five years, and to the last he worked to have established a more uniform and simple classification of these changes.

The untiring devotion of Dr. Clay to the welfare of his patients, his constant efforts to provide more effective ophthalmologic service and treatment, his ready application of newer and better methods, were all representative of his dogged, ever searching spirit, which never ceased fighting when confronted with a desperate case.

Perhaps the greatest contributions that Dr. Clay made to medicine and to society were his interest in the welfare of the poor and underprivileged and his love and understanding of the country folk, manifested not only in free clinics at Grady Hospital and Emory University Hospital but also at his farm home, where on Sunday afternons he would often see the poor of his neighborhood, providing any necessary hospitalization at his own expense.

Dr. Clay possessed a magnificent physique and a commanding appearance. He was a forceful and enthusiastic speaker and was a frequent and popular guest at many postgraduate and society meetings. His cordiality, friendliness and winsome smile attracted people.

Dr. Clay loved sports and outdoor life. His favorite pastimes were hunting and fishing; but his obsession and hobby was his nearby farm, where he took great pride in his herd of registered Hereford cattle.

In 1915 Dr. Clay married Miss Eleanor Hall Solomon, of Macon, Ga. Two children, Grady Clay Jr., of Louisville, Ky., and Mrs. Eleanor Clay Calhoun, of Atlanta, Ga., and 3 grandchildren survive.

Dr. Clay was vice chairman of the Section of Ophthalmology of the American Medical Association and was a former member of the American Board of Ophthalmology. He was a member of the Methodist faith and a liberal contributor to his country church. His college fraternity was Phi Delta Theta, and he held membership in the national scholastic societies of Phi Rho Sigma, Sigma Xi, Phi Beta Kappa and Omicron Delta Kappa.

We who had worked daily by the side of Dr. Clay for nearly thirty years knew his worth as a physician, humanitarian, teacher and friend. Taken in the prime of life, with many useful years before him, his loss is tremendous. To his legion of friends, a hero has fallen!

"He was a man, take him for all and all.
I shall not look upon his like again."

F. PHINIZY CALHOUN, M.D.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Conjunctiva

CHOICE OF SULPHONAMIDE IN THE TREATMENT OF OPHTHALMIA NEONATORUM. ARNOLD SORSBY and E. E. HOFFA, Brit. J. Ophth. **29:** 141 (March) 1945.

On the basis of 333 cases of ophthalmia neonatorum treated with a standard dose of five sulfonamide compounds, it is concluded that the least tolerated drug is sulfanilamide and that sulfapyridine is less well tolerated than sulfamezathine, sulfathiazole or sulfadiazine.

In their efficacy against the infection, as distinct from their tolerance by the babies, these five substances are not strikingly different.

With the standard dose employed in this series, some 30 to 40 per cent of infants show clinical cure within three days. Well over 80 per cent of the total are cured by the end of eight days' treatment.

Gonococcic ophthalmia neonatorum responds more readily than other varieties of ophthalmia. Cases showing inclusion bodies respond satisfactorily. An initial severity does not affect the course unfavorably. Many severe cases clear rapidly. Irrespective of the causal organism, some 15 per cent of cases show a sluggish or poor response. The routine management of cases is described.

W. ZENTMAYER.

THE SOCIAL AND MEDICAL PROBLEMS OF PHLYCTENULAR DISEASE IN DUBLIN. J. B. MCAREVEY, Irish J. M. Sc., July 1944, p. 201.

The object of the inquiry was to determine the trend of phlyctenular disease in Dublin, the age and sex incidence, the seasonal incidence, the types of the disease and the occupation of parents of children suffering from the disease. The information was obtained from an analysis of 2,470 new cases at the Royal Victoria Eye and Ear Hospital, Dublin. The periods selected represent World War I, the present war and a normal period immediately before the present war. The study warrants the conclusion that basically phlyctenular disease is a manifestation of malnutrition. It is a disease of the poorer classes, in whose diet the essential proteins necessary to growth and normal development are practically absent, the only source of these substances available to most of the children being milk, in limited quantities; as a result, they suffer from a low grade malnutritional anemia, with a deficiency of some essential vitamins.

It is interesting to note that the evidence of tuberculous infection was positive. 1. The reaction to the tuberculin test was positive in 85.9 per cent of children (13 per cent of controls). 2. Roentgenograms of the chest showed positive evidence in 37.3 per cent of children (20 per cent of controls). 3. There was a history of contact in 5.5 per cent (and of possible contact in 2.9 per cent). 4. The incidence of sanatorium care was 11.8 per cent. The nature of the tissue reaction points to an allergic response.

W. ZENTMAYER.

Congenital Anomalies

BILATERAL PARTIAL ECTASIA OF THE NERVE HEAD WITH PERIPAPILLARY ECTASIA. I. S. MACGREGOR, Brit. J. Ophth. **28:** 618 (Dec.) 1944.

The case described is one of partial ectasia of both optic disks with complete peripapillary ectasia. The disks were not completely excavated. The picture is remarkably similar to the late results of traumatic avulsion of the optic nerve with preservation of the continuity of the vessels except that glial proliferation at the nerve head is usually pronounced in cases of proved avulsion. The condition is regarded as a congenital anomaly of the optic disk. It may be a rare form of birth injury resulting in partial avulsion of the optic nerve rather than a developmental failure at the disk.

The article is illustrated.

W. ZENTMAYER.

CONGENITAL DEFECTS AND RUBELLA. Brit. M. J. **1:**635 (May 5) 1945.

In Australia 109 cases of congenital defects associated with maternal rubella have been reported. Reese, Erickson and Simpson report 16 additional cases in other countries. "The main points of agreement in the published data appear to be: (*a*) that the association is with rubella and not with other transmissible diseases (though not without exception); (*b*) that the risk of congenital defect is greatest if the rubella occurs in early pregnancy (i. e., within the first three months) and (*c*) that there are infants with congenital defects in which no link with a maternal transmissible disease can be traced. The general inference is that the unknown virus of rubella (with virulence possibly enhanced in the war years) is showing the preference of certain viruses for developing embryonic tissue. This it does by attacking the foetus via the placental circulation just at a time when important developmental changes are taking place in the foetal heart and eye. The high incidence of congenital heart disease suggests to these observers that the rubella virus has a primary affinity for vascular tissue, the lens damage being explained by possible indirect action through the hyaloid artery."

The author asks whether the association between presumed rubella and congenital defects is a significant one or whether it arises from pure chance. The question also arises: Was the maternal disease rubella? According to the author, in some cases the diagnosis was in retrospect unsatisfactory and in others hardly justifiable. He believes that the possibility of a chance association between congenital defects and true maternal rubella cannot be excluded and suggests that a systematic investigation of rubella in pregnant women be instituted.

ARNOLD KNAPP.

Cornea and Sclera

A FREQUENT AND DEFINED TYPE OF KERATITIS. E. ROMERO, Arch. Soc. de oftal. hispano-am. **3:** 458 (Nov.-Dec.) 1943.

The author describes a condition of the cornea produced by alcohol vapors, entirely different from the burn produced by direct action of

the liquid. The lesion produced is a superficial, faint central erosion of the epithelium, with no opacity. It takes the stain poorly but can be detected by the ridge formed around it by the peripheral zone of normal epithelium. The patient with such a lesion comes to the oculist complaining of pain, sensation of a foreign body, photophobia, blepharospasm, congestion and lacrimation, without pathologic antecedents, a history of injury from a foreign body or any apparent corneal lesion. There is a history of exposure to alcohol.

H. F. CARRASQUILLO.

PHLYCTENULAR KERATOCONJUNCTIVITIS OBSERVED IN THE GAFFREE AND GUINLE OUTPATIENT DEPARTMENT IN SANTOS. D. LIVRAMENTO PRADO, Arq. brasil. de oftal. **5:** 51 (April) 1942.

Four hundred and eight patients with phlyctenular keratoconjunctivitis were observed in the outpatient department of this institution; 202 children were boys and 180 girls, and 26 patients were adults. The etiologic factors are discussed.

In 1936 the author performed Pirquet's cutaneous test in 36 cases of lymphatic keratoconjunctivitis and obtained a positive reaction in 100 per cent. A roentgenogram of the lungs was taken in 14 cases, the results being as follows: In 52 per cent of the 14 cases there were incipient pulmonary disturbances, the lungs being normal in the remaining 48 per cent.

Therapy consisted in injections of Gaduzan, 2 cc.; calcium gluconate in a 10 per cent solution; tuberculin, and the usual ocular treatment with such means as strong protein silver, Noviform (a bismuth preparation) and vapor baths.

Progressive improvement was noted, and a cure was effected within twenty to thirty days. In 6 of the cases in which no pulmonary alterations were noted rigorous treatment with preparations of vitamins C and B was instituted, cure being effected in twelve days.

This seems to show that lymphatic keratoconjunctivitis may be due to an avitaminosis, although the possibility of a tuberculous causation seems to be definitely established.

M. E. ALVARO.

Experimental Pathology

EXPERIMENTAL PHOTO-RETINITIS. J. C. ECCLES and A. J. FLYNN, M. J. Australia **1:** 339 (April 15) 1944.

The authors, carrying further the investigations of Verhoeff, Bell and Walker (Pathological Effects of Radiant Energy on the Eye, *Proc. Am. Acad. Arts & Sciences* **51:** 630, 1916) exposed the retina of anesthetized rabbits to direct rays of the sun, admitted through a round hole in a metal plate fixed close to the pupil. Lesions obtained at first were very small, and to enlarge them one tube of a Zeiss binocular was used as a telescope. A formula was devised to calculate the calories per square centimeter per minute at the site of the retinal image, and exposures were carried out with and without absorption filters. The eyes were examined ophthalmoscopically and, later, microscopically.

It was found that with thirty seconds' exposure lesions were produced when the radiation was above 50 calories per square centimeter per minute but not when the radiation was below 40 calories. Ultraviolet rays were absorbed and did not reach the retina. Microscopic examination revealed an amount of destruction of cells proportionate to the radiation.

The authors found that radiation of an intensity as high as 100 calories per square centimeter per minute requires several seconds to produce lesions, and they conclude that rapid glances at the sun are therefore innocuous. They also point out that protective glasses with high absorptive powers for visible rays may be dangerous when used for viewing the sun if they transmit infra-red rays.

G. M. BRUCE.

General Diseases

TUBERCULIN SENSITIVITY AND OCULAR PROCESSES. M. F. VIGNOLI and C. GARBINO, Arch. de oftal. de Buenos Aires **18:** 713 (Dec.) 1943.

The study of the index of tuberculous infection carried on extensively in various countries in the past several years has altered the belief that this infection occurs only in very early life. In Montevideo the maximum incidence of infection is reached at the age of 30 years. Fifty per cent of the school children give a negative reaction to tuberculin in a dilution of 1 : 10 in the Mantoux test.

In Argentine, of 37,139 conscripts, 41 per cent gave a negative reaction. In Buenos Aires, in 1940, according to the studies of Raimondi and associates, 40 per cent of the youth from 14 to 20 years of age were found free from infection. It is therefore established that the tuberculin allergy may help in the diagnosis of tuberculous ocular conditions not only in children but in adults.

To establish a state of allergy, a negative response to the Mantoux intradermal test, to first and second concentrations of purified protein derivative or to a 1 : 10 dilution of Koch's old tuberculin is necessary. A maculopapule larger than 10 mm. is considered a positive reaction. If smaller, the reaction is considered doubtful. If the primary infection is of recent occurrence, the reaction may be negative, and tests must be repeated thirty or sixty days later.

Studies were made on 75 patients. The threshold of allergy was determined, and roentgenographic studies of the chest were made on these patients. New determinations of the threshold were made at various intervals, and a graphic curve of the sensitivity to tuberculin was traced.

The authors give in detail the technic used in their tests and list the results obtained on the 75 patients studied, including 19 ocular conditions which might have a tuberculous origin. Of the patients, 27 were men and 48 women. The ages ranged from 10 months to 52 years, and the majority were between 15 and 30 years of age.

The number of anergic subjects was 9, or 10.2 per cent. Of the allergic patients, 91.6 per cent were tested for hyperergy, and 72.7 per cent gave positive reactions to dilutions above 1 : 1,000,000.

In cases of phlyctenular keratoconjunctivitis the threshold ranged from a positive reaction to a dilution of 1 : 10,000,000,000 and a negative

reaction to a dilution of 1 : 10. For 25, out of a total of 35 patients, the threshold concentration was above 1 : 1,000,000.

The existence of hypersensitivity to tuberculin in the presence of a pathologic process in the eye is not positive proof of a bacillary origin but is information to be added to the clinical examination. However, when the threshold is determined in the way advocated by the authors and some correlation is shown between the sensitivity and the lesion, the one being increased with aggravation of the other or diminished when the process improves, the disease in all probability is tuberculosis. In contrast to the cases of intense hyperergy, when the reaction is negative to concentrations of 1 to 10, tuberculosis may be excluded. If the case is one of hypoergy the diagnosis of tuberculosis is in doubt.

H. F. CARRASQUILLO.

Hygiene, Sociology, Education and History

THE ANTIQUITY OF OPHTHALMOLOGY. W. B. INGLIS POLLOCK, Brit. J. Ophth. **29:** 252 (May) 1945.

This interesting historical article does not lend itself to abstraction. In brief, as stated by the author, it has been shown that ophthalmology was in existence in Egypt during the days of the Old Kingdom, before 3,000 B. C., and also in Mesopotamia between 2000 and 1500 B. C. It was the first specialty to be set up, by reason of the serious results of the various, extremely frequent, diseases of the eye which oculists were required to treat, and was an effort then, as now, to prevent them from the dire results of failure.

W. ZENTMAYER.

INDUSTRIAL OCULAR LESIONS AS COVERED BY THE ARGENTINE LAW. JOSÉ A. SENÁ, Arq. brasil. de oftal. **7:** 213 (Dec.) 1944.

A historical summary of the legislation for industrial accidents to the eyes is presented. Various statistics on industrial ocular accidents in Argentina and in the United States are given, those of Argentina being presented in greater detail. The occupational diseases, defined in chapter 11, article 145, of the Argentine law as being "those due exclusively to the work undertaken by the patient in the exercise of his occupation," are discussed. These diseases are divided into three groups: (1) purely local disorders which may have much to do with industrial accidents—the external ocular diseases; (2) ocular lesions resulting from poisoning or a general infectious condition which may be imputed to work, and (3) visual disturbances resulting from bodily fatigue. In the last group miners' nystagmus and visual alterations due to prolonged eyestrain in certain occupations are included. The following subjects are considered in detail: external ocular diseases; the eye and occupational poisoning; trachoma, ocular tumors, ocular syphilis, ocular tuberculosis, exophthalmic goiter and retinal detachment in relation to industrial accidents; ocular traumas and their general repercussion, and ocular traumatic neuroses and psychoses. The author comments on the Argentine laws relating to industrial accidents.

M. E. ALVARO.

Injuries

PENETRATING INJURIES OF THE EYE. W. F. MONCREIFF and K. J. SCHERIBEL, Am. J. Ophth. **28:** 1212 (Nov.) 1945.

This is a statistical study. Two practical conclusions are drawn; namely, that 20 per cent of penetrating injuries could be eliminated, or at least minimized, by eliminating glass from the domestic economy and that in a smaller percentage prompt enucleation should be done.

W. S. REESE.

NON-MAGNETIC INTRAOCULAR FOREIGN BODIES. Editorial, Brit. M. J. **1:** 228 (Feb. 17) 1945.

Aluminium is being used increasingly in the manufacture of projectiles, and except for shell and bomb fragments most missiles may now be regarded as nonmagnetic. This was described by Savin in a Hunterian Lecture two years ago, and this author has now brought the subject up to date in a paper recently read before the Royal Society of Medicine. The proportion of magnetic and nonmagnetic foreign bodies in the eye is 1:6, and this is still more unfavorable in air raid casualties, in which the proportion is 1:9. The attending infections were favorably influenced by the use of sulfonamide compounds, but the problem of these retained foreign bodies is increased by ignorance of the reaction of the eye to aluminium.

Savin has made a number of experiments to study the reaction of the eye to aluminium. He finds that pure aluminium may be completely absorbed but more often the fragment becomes coated with a white deposit of aluminium hydroxide or with fibrin and gelatinous material. Changes in the lens and vitreous were late results in almost all cases, and there was evidence of retinal damage. It is clear that aluminium is not inert and that its removal from the eye is difficult. It is essential that an accurate localization of these nonmagnetic foreign bodies be made, and a successful forceps extraction is more likely in the anterior segment of the eye than in the posterior segment. Savin concludes that until there is an improvement in technic the removal of these bodies should only be attempted in cases in which clinical observations show the foreign body to be deleterious.

ARNOLD KNAPP.

Lacrimal Apparatus

DACRYOCYSTORHINOSTOMY: THE DUPUY DUTEMPS–BOURGUET–VALLE PROCEDURE. E. J. J. LAGOS, Arch. de oftal. de Buenos Aires **18:** 639 (Nov.) 1943.

The author gives an account of his experience with the classic technic. In his opinion, Valle has simplified the procedure with the instruments he has designed, the time of operation being shortened and less instruments being needed than with any other method.

Lagos advocates the operation of dacryocystorhinostomy instead of extirpation of the lacrimal sac, the latter to be done in cases of new growths, tuberculosis or too small a sac. Previous conservative treat-

ment with probing and irrigations is recommended. Intranasal examination before the operation is important.

The author has performed the operation in more than 100 cases, with gratifying results. In only 3 cases did profuse intranasal hemorrhage occur, and in 1 case there was slight suppuration. A detailed description is given of the technic of the operation, some of the Dupuy Dutemps instruments and those designed by Valle being employed. The osteotome is preferred to the burr or the chisel and hammer, being less liable to injure the nasal mucous membrane.

The indications and contraindications to the operation are given.

H. F. CARRASQUILLO.

Lids

TOTAL RECONSTRUCTION OF THE UPPER LID (BLEPHAROPOIESIS). W. L. HUGHES, Am. J. Ophth. **28:** 980 (Sept.) 1945.

Hughes comments on the importance of the upper lid in protecting the globe and discusses the reconstruction of the lid. He reports a case and describes all the stages of repair, using numerous illustrations.

W. S. REESE.

MER BROMIN [MERCUROCHROME] IN TREATMENT OF BLEPHARITIS. J. DE P. XAVIER, Arq. brasil. de oftal. **7:** 232 (Dec.) 1944.

Owing to the difficulty of obtaining the Pyoktanin (gentian violet medicinal) drugs in pencil form, the author requested a chemist to make up a merbrom (mercurochrome) pencil, consisting of pure acacia, distilled water and approximately 80 per cent of merbromin. This was used in 10 cases of ulcerative blepharitis, 9 cases of crustal blepharitis and 8 cases of squamous blepharitis. Daily applications were made and satisfactory results obtained. Squamous blepharitis was cured after ten to fifteen treatments, the more serious forms (ulcerative blepharitis) requiring further applications in order to obtain the same results. A bibliography is included.

M. E. ALVARO.

Neurology

OCULAR NEUROVEGETATIVE SYSTEM IN RELATION TO OCULAR TENSION AND PREGNANCY. F. VIDAL and S. A. DURANDO, Arch. de oftal. de Buenos Aires **19:** 32 (Jan.) 1944.

The hypothalamus controls the visceral functions by two different mechanisms: The lateral part of the organ is the chief regulating center of the sympatheticoadrenal system, and the medial part, of the parasympatheticohypophysial system. Ocular tension is physiologically controlled by these two systems, being increased by the first and decreased by the second. During normal pregnancy the parasympatheticohypophysial system is more active, and so the ocular tension during this period stays at the lower normal levels, or even below.

One hundred normal pregnant women between the ages of 15 and 40 were examined. The Schiøtz and MacLean tonometers were used.

The measurements ranged from 15 mm. Schiøtz and 22 mm. MacLean, in 56 per cent of patients, to 11 mm. Schiøtz and 14 mm. MacLean, in 7 per cent.

H. F. CARRASQUILLO.

THE CENTRAL SCOTOMA AS AN EARLY SYMPTOM IN THE DIAGNOSIS OF INTRACRANIAL CONDITIONS. A. GARCIA MIRANDA, Arch. Soc. oftal. hispano-am. **4:** 30 (July-Aug.) 1944.

Central scotoma is a frequent symptom which is not properly evaluated. It is usually taken as a sign of retrobulbar neuritis, without regard to the fact that it may be an early indication of an intracranial condition then amenable to treatment.

In cases of tumor of the frontal lobe, hypophysial neoplasm, arteriosclerotic changes in/or aneurysm of the internal carotid artery, optochiasmic arachnoiditis and meningioma of the lamina cribrosa of the ethmoid bone, a central scotoma may occur early in the course of the disease.

H. F. CARRASQUILLO.

MOTOR-SENSORY OPHTHALMOPLEGIA. W. DUQUE ESTRADA, Rev. brasil. de oftal. **2:** 135 (March) 1944.

Estrada discusses the neuropathologic syndromes caused by lesions of the motor and sensory nerves in their orbital course. He divides them into (1) syndrome of the sphenoid fissure, either with or without amaurosis; (2) syndrome of the petrous-sphenoid junction (Maurice-Jacod), and (3) syndrome of the external wall of the cavernous sinus (Foix).

The author reports the case of a man with a syndrome of the sphenoid fissure. He interprets the significance of the motor, sensory and visual disorders as well as the presence of exophthalmos for the diagnosis of a lesion of the nasal nerve due to a tumor of the sphenoid fissure. In the case he reports the laboratory, roentgenographic, otorhinolaryngologic and early clinical examinations did not aid in diagnosis. Roentgen therapy failed. A clinical diagnosis of blastoma of the sphenoid fissure, made late in the course of the disease, was verified at necropsy.

W. ZENTMAYER.

Operations

RECONSTRUCTION OF THE LIDS. W. L. HUGHES, Am. J. Ophth. **28:** 1203 (Nov.) 1945.

Hughes discusses surgical reconstruction of the lids. He concludes that normal structures of the lid should be used as replacement tissue or, if such tissue is not obtainable, tissue as similar to the original as possible. A second choice is (*a*) for the skin of the lid, full thickness skin from the cephaloauricular angle, to be used as a free graft, or a pedicle graft; (*b*) for the conjunctiva, mucous membrane from the mouth or thin split skin, and (*c*) for the tarsus, cartilage from the ear or rib.

W. S. REESE.

USE OF APONEUROSIS OF GASTROCNEMIUS MUSCLE FOR PLASTIC OPERATIONS ON THE CONJUNCTIVA FORNIX. G. BURSUK, Vestnik oftal. **23:** 13, 1944.

This paper is a preliminary report.

Bursuk used the aponeurosis of gastrocnemius muscle for plastic operations on the conjunctiva fornix, in 2 cases for partial and in 3 cases for complete restoration of the conjunctival sac. This material was found to be adequate, as it is firm, does not shrink and is plastic enough to take a given shape and often complete union with the conjunctiva takes place. The color of the transplant changed in one and a half to two weeks and took on the color of the conjunctiva.

A prosthesis was usually put in the day after the operation, so that the transplant could take the shape of the prosthesis. The flap was taken from the middle third of the muscle; the shape of the incision was semielliptic (for prevention of opening of the sutures), with the base below and lateral to the tibial crest.

The results are reported in case histories. O. SITCHEVSKA.

Orbit, Eyeball and Accessory Sinuses

A NEW METHOD AND APPLIANCE FOR GRAFTING EYE SOCKETS. H. P. PICKERILL, Brit. M. J. **1:** 596 (April 28) 1945.

To avoid the great difficulty in getting a glass eye to fit the socket one has made, the author has reversed the process and makes the socket fit stock-sized glass eyes. A stock-sized glass eye is first obtained; this is enlarged with wax and duplicated in acrylic resin by taking molds in stent, plaster or gelatin. Two holes are drilled through this mold, of the same size as the nozzle of a Record syringe. One hole is drilled exactly in the center of the pupil. Into this hole is fitted a pin about 1½ inches (3.8 cm.) long, with a little shoulder, which prevents it from going too far in. After the socket has been prepared in the usual manner a one-half thickness of skin graft is cut with the dermatome, fixed on the acrylic mold and inserted into the socket. The pin is inserted and fixed with strips of strapping from forehead to cheek and nose, so that the pin, which is exactly in the place of the future pupil, will be in the correct position. The lids are then sutured. After ten days some discharge appears. The pin is removed, and the socket is gently irrigated through the holes provided in the socket. The pin and strapping are then replaced. The appliance is left in position for one month; it is then removed every other day for cleaning and is reinserted, pressure being kept up by elastoplast strips. In not less than two months the appliance can be discarded, and the stock glass eye will be found to fit perfectly.

There is no coordinated movement; in a grafted eye, movement has never been possible. The method gets over the almost insuperable difficulty of having a special eye made for every grafted socket.

ARNOLD KNAPP.

Refraction and Accommodation

CATMIN LENSES. S. KAMELLIN, Am. J. Ophth. **28:** 993 (Sept.) 1945.

Kamellin describes the catmin lens as an image-minifying lens, of special value in certain cases of unilateral aphakia. He reports 10 cases from the files of the late Dr. S. R. Gifford.

The advantage of catmin lenses lies in the fact that they are reversed telescopic lenses which are of value in certain cases of unilateral aphakia in children and in adults in which contact lenses cannot be used to maintain binocular vision. The disadvantages of catmin lenses are that cosmetically their appearance leaves much to be desired and the field of vision with their use is restricted about 23 per cent.

The author reaches the following conclusions: Catmin lenses are of benefit in many cases for the maintenance of binocular vision and may be added to the armamentarium of the ophthalmologist, to be used in cases in which the patient does not object to the appearance of the lens and does not object to the restriction in the field of vision and in which contact lenses cannot be prescribed. W. ZENTMAYER.

Retina and Optic Nerve

THE END RESULTS OF OPERATIONS FOR DETACHMENT OF THE RETINA WITH A FOLLOW-UP OF FIFTY-FIVE SUCCESSFUL CASES. M. L. HINES, Brit. J. Ophth. **28:** 575 (Nov.) 1944.

Hines has made a full analysis of the cases of 120 patients with detachment of the retina who were operated on by the end of 1942, with successful results in 50, or 41.66 per cent. If 49 patients who were bad risks are omitted, the percentage is 49.29. Thirteen of the patients discharged with the retina in place and a full field of vision returned at intervals varying from three weeks to six months with a history of sudden loss of vision and the retina again detached. Two patients sent out as representing failures returned later with the retina in place and a full field of vision. In 1 patient the redetachment took place three years after the operation. Further operation was unavailing. This patient was 9 years of age and had been operated on previously elsewhere, without success. Four patients had aphakia. In all of them the operation was a failure. Twenty of the series had secondary operations, with 3 successes. A definite history of trauma was elicited from 13.83 per cent. Forty per cent were myopic.

Most of the patients received surface diathermy with Weve's applicator, the current varying from 110 to 120 milliamperes, followed by diathermy puncture and removal of as much subretinal fluid as possible with a "sucker." Further analysis with respect to such factors as age, position of holes, final vision and visual field is made.

W. ZENTMAYER.

RETINOSIS ACCOMPANYING NIGHT BLINDNESS. A. MOREU, Arch. Soc. oftal. hispano-am. **4:** 115 (Jan.-Feb.) 1944.

So-called pigmentary degeneration of the retina is not a well established nosologic entity. There are several varieties, one of which is acquired. In the beginning the condition in the retina has a physiologic basis; the anatomic changes come later.

Studies were conducted on the classic familial type. Observations were made on children with the disease, and experiments were carried out on animals.

Twenty-two children, 10 boys and 12 girls, from 10 to 18 years old, were studied. Anatomically, 2 patients presented peripheral lesions of the retina and 6 showed attentuation of the retinal arterioles. Fourteen were apparently normal. The children with anatomic lesions showed contracted fields, while the apparently healthy children exhibited changes in the threshold for dark adaptation.

Determination of the chronaxia of the retina indicated a normal reaction in the children with no anatomic lesions. This tended to prove that the factor giving rise to the phenomenon of night blindness has its seat in the layer of the rods and cones, in the choriocapillaris and in the pigment epithelium.

The first symptom of the disease in these children was night blindness, denoting that some disturbance in the metabolism of the visual purple was taking place. General physical examination showed disturbance in the endocrine–sympathetic nervous system. The vitamin A content of the blood was, however, normal.

The investigator has formulated a hypothesis for the causation of pigmentary degeneration of the retina. The beginning of the process, according to him, is due to some dysfunction of the hypothalamus. Experiments on animals partly proved his assumption.

H. F. CARRASQUILLO.

Trachoma

SULFONAMIDE THERAPY OF TRACHOMA. J. A. SENÁ, Arch. de oftal. de Buenos Aires **18:** 703 (Dec.) 1943.

The use of the sulfonamide compounds has been one of the greatest advances in the treatment of trachoma in the last fifty years. These drugs have given first place to the general treatment of the disease, with the local therapy relegated to a secondary position.

The author relates the history of the use of the sulfonamide drugs in the treatment of trachoma. He made a trial treatment of 2 patients with a severe form of the disease and concluded that the medication was effective, and since then he has continued its use. He has obtained the best results when the disease had a corneal predominance. The drug is administered by mouth and locally in the form of a 10 per cent solution of sodium sulfathiazole and a 30 per cent solution of the sodium salt of sulfacetimide. He attributes to the oral administration a striking effect on the subjective symptoms.

For the rapid disappearance of the conjunctival lesions (follicles) he still uses the copper sulfate pencil as a supplementary measure. Although he is enthusiastic over this new treatment of trachoma, he states that it is yet too early to speak of it as producing a definite cure.

H. F. CARRASQUILLO.

Society Transactions

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Rudolf Aebli, M.D., *Chairman*

Truman Boyes, M.D., *Secretary*

March 18, 1946

INSTRUCTION HOUR

Clinical-Pathologic Correlations in Cases of Enucleation of the Globe.

DR. JOSEPH LAVAL.

The author correlated the clinical histories with the pathologic changes in the enucleated eyeball demonstrated in the following cases:

CASE 1.—The lens was found to have been injured at operation for acute glaucoma.

CASE 2.—The clinical diagnosis was melanosarcoma of the choroid, and examination of the eyeball showed that the sarcoma had perforated the globe and extended into the sheath of the optic nerve.

CASE 3.—A patient aged 69 had been blind in one eye since the age of 18 as the result of trauma. The clinical diagnosis was phthisis bulbi, but the atrophic eyeball showed the presence of sarcoma of the choroid.

CASE 4.—The clinical diagnosis was sarcoma of the choroid, and examination of the eyeball showed that the tumor had perforated the globe and a large extraocular mass was present.

CASE 5.—The clinical diagnosis was sarcoma in the macular region, but a subretinal hemorrhage was observed on examination of the enucleated eyeball.

CASE 6.—The eyeball of a patient aged 28 was enucleated for sarcoma of the macular region. The clinical diagnosis was confirmed on examination; the tumor was very small.

CASE 7.—In a case of acute glaucoma examination of the eyeballs showed a melanosarcoma with signs of old glaucoma.

CASE 8.—The eyeball was enucleated for tumor of the iris, but examination revealed a benign cyst of the stroma of the iris.

CASE 9.—In a case with a history of inflammation and increased tension following operation for cataract a diagnosis of exudate in the anterior chamber was made, but examination revealed the presence of a downgrowth of epithelium.

CASE 10.—In a case in which operation had been performed for congenital cataract and absolute glaucoma had then developed, twenty-nine years before, examination of the enucleated eye showed a hyaline membrane on the iris.

CASE 11.—For an 18 month old child a diagnosis of endophthalmitis had been made, but microscopic examination of the eye showed glioma, which had extended into the anterior chamber.

CASE 12.—For a 9 month old child a diagnosis of glioma had been made, and examination of the eyeball proved this to be correct.

CASE 13.—In a child 4 years of age the mother had noticed the appearance of a "cat's eye," and a diagnosis of glioma had been made, which was verified on examination.

REPORT OF CASES

Removal of a Foreign Body from the Orbit with Aid of the Berman Localizer. DR. SAMUEL WENGER, Flushing, N. Y.

E. S., a 5 year old boy, was struck in the right eye with the end of a small paintbrush on Jan. 1, 1946. The injury was followed by pronounced swelling of the right upper lid, entirely closing the palpebral fissure. On January 15, two weeks after the accident, the patient was referred to me for consultation. A roentgenogram taken at this time disclosed the presence of a large intraorbital foreign body, about 1½ inches (3.8 cm.) long which corresponded to the metallic end of the paintbrush containing the bristles. There was no pain or inflammation. The eyeball was fixed and rotated downward. Vision was normal.

The pateint was admitted to the hospital on January 16. With the child under general anesthesia, an incision was made horizontally across the upper lid just below the superior orbital rim. At no time could the foreign body be seen or palpated. After probing for at least half an hour, during which encapsulated pus was encountered, I inserted the tip of a Berman localizer; the foreign body was instantly located and its removal readily accomplished.

The case is of interest in that there was so much difficulty in locating such an unusually large foreign body. The metal was nonmagnetic, and it is felt that the results obtained with the Berman Localizer were gratifying.

DISCUSSION

MR. SAMUEL BERMAN: I have here the foreign body which is the subject of this case report. As you can see, it is about ⅛ inch (3 mm.) in diameter and 1 inch (2.54 cm.) in length; and for the purpose of this demonstration it has been attached to the thin wooden handle of the brush from which it had originally broken off. Although this foreign body is of aluminum, and therefore nonmagnetic, it was readily detected with the probe of the Localizer because of its relatively large size and the fact that the incision was initially placed with sufficient accuracy to bring the probe within easy detecting range. The localizer which was used in this case, and which is here demonstrated, has two indicators: a meter for visual and a loudspeaker for auditory indication. I shall demonstrate what happens when the probe approaches the foreign body (demonstrating). The closer the foreign body is approached, the higher the meter indicator goes; simultaneously, the tone from the loudspeaker rises in pitch. The nonmagnetic foreign body demonstrated here is detected from a distance of about ¼ inch (6 mm.). In general, nonmagnetic foreign bodies of relatively small dimensions, that is, spherical bodies smaller than 3 mm. in diameter, occurring intraocularly will not be detected with the localizer. The detecting range for larger nonmagnetic foreign bodies is from one to two times the diameter of the foreign body.

The sensitivity of the Localizer to iron or steel, however, is very high, the detecting range being about ten times the diameter of the foreign

body; that is, a mass 1 mm. in diameter will be detected from a distance of 10 mm., and a mass 2 mm. in diameter, from a distance of 20 mm.

I have several samples of magnetic foreign bodies with which I shall demonstrate the use of the Localizer for foreign bodies. The one which I now have in my hand (demonstrating) is of common steel, ⅛ inch in diameter and about ¼ inch in length. This fragment is detected from a distance of well over 1 inch. This sponge with an open slit, representing a wound in which a small foreign body has been placed, will illustrate the manner in which the Localizer is used in general surgery or in the removal of an intraorbital foreign body (demonstrating). The probe is inserted within the wound, and the tip is moved about so as to scan all the interior surfaces. The point at which the maximum response is noted indicates the position of the foreign body and determines the direction in which to proceed with further dissection.

To illustrate the use of the Localizer in work with intraocular foreign bodies, I have this artificial eye, against the inner surface of which is glued a tiny magnetic foreign body, made of violin E string wire, 0.25 mm. in diameter and a 0.5 mm. in length. This is about the smallest size of intraocular foreign body ordinarily encountered (demonstrating). I get a good response through the glass, which represents the average thickness of the sclera. As I move the tip of the probe along the surface, the effect varies. The point where the peak response is obtained is the point of closest approach. I shall now move the tip of the probe about 0.5 mm. to one side of this point. The sound changes abruptly, although the movement is probably not visible to persons in the back of the room. This is what is termed "pinpoint" localization, expressing the high accuracy obtainable with this device.

Sterile conditions are obtained by applying a rubber jacket over the probe. This jacket is of surgical rubber and may be boiled or autoclaved. It in no way interferes with the detecting action.

For work with intraocular foreign bodies, the outer shield of the probe is generally removed, thus reducing the diameter of the tip and permitting closer approach of the sensitive element to the surface, with resulting still greater sensitivity and accuracy. The bare element is then covered only with the sterilizable rubber jacket.

DR. TRUMAN L. BOYES: How does the Localizer react to lead bodies?

MR. SAMUEL BERMAN: The Localizer does not react as strongly to nonmagnetic as to magnetic foreign bodies. A nonmagnetic foreign body has to be fairly large in order to produce a reaction at any appreciable distance.

DR. JOSEPH LAVAL: The localization of magnetic and nonmagnetic foreign bodies was well demonstrated three years ago at Mount Sinai Hospital, in an attempt to localize a small piece of copper. A roentgenogram was of no help in deciding whether it was localized in the sclera or in the orbit.

DR. ARNOLD KNAPP: How is the action with nonmagnetic foreign bodies explained?

MR. SAMUEL BERMAN: In the detection of nonmagnetic foreign bodies, the reaction occurs through what is known as eddy currents.

The alternating magnetic field about the probe sets up these small currents within the mass of metal being searched for. These currents, in turn, produce local magnetic fields about the metallic mass, which react with the field of the probe and thereby cause the changes, resulting in the sound which was heard.

DR. WENDELL L. HUGHES, Hempstead, N. Y.: May lateral pressure on the end of the tip give a false reading when no foreign body is present?

MR. SAMUEL BERMAN: Yes. In using the instrument with the outer shield in place, lateral pressure must not exceed 1 pound (373 Gm.). Such pressure is, of course, never approached in ophthalmic work. In general surgery, however, when one is probing in a bony area, one must not use the probe as a pry or the pressure limits may be exceeded and a false response, or pressure error, be produced (demonstrating). I am now pressing against the tip of the probe with about ½ pound (186 Gm.) pressure, without any effect. I now increase the pressure, and a response similar to that from a foreign body is obtained. One must be especially careful when using the probe with the shield removed, as is recommended for work with intraocular foreign bodies. For such use, the bare sensitive element is covered only with the sterilizable rubber jacket to exclude dirt and moisture, and any pressure amounting to more than the barest contact against the surface of the globe may produce pressure errors. The degree of pressure error is readily determined by the operator by applying the tip of the probe to his gloved hand with approximately the same pressure as that used on the surface of the eye.

PAPERS OF THE EVENING

Binasal Hemianopsia. DR. J. IGERSHEIMER, Boston.

This paper will be published in a future issue of the ARCHIVES.

DISCUSSION

DR. THOMAS H. JOHNSON: I regret I did not have the privilege of reading Dr. Igersheimer's paper before his presentation.

Binasal hemianopsia is a rare finding. At the Neurological Institute of New York, my associates and I took 3,346 visual fields on patients who had neurologic disturbances; of these, 230 showed defects in the visual fields. In only 1 case was there binasal hemianopsia. I have seen only 3 cases of binasal hemianopsia in my entire medical career. In 2 of them there was no autopsy. In these 2 cases the cause of the hemianopsia was believed to be calcification of the internal carotid arteries. The diagnosis was based on roentgenologic examination and the absence of any other neurologic findings. The relation of the internal carotid arteries to the chiasm varies in different persons. Schaeffer (Some Points in the Regional Anatomy of the Optic Pathway, with Special Reference to Tumors of the Hypophysis *Anat. Rec.* **28:** 243, 1925), in a dissection of 125 cadavers, demonstrated that the chiasm varies in its relation to the surrounding structures. He observed that the chiasm may lie in front of, directly over or behind the hypophysis. In cases in which the chiasm is located well posteriorly the optic nerve is rather long. A slide was shown of a drawing of an aneurysm of the circle of Willis, demonstrating the relation to the surrounding structures

of the internal carotid artery as it comes from the cavernous sinus and divides into the anterior and posterior cerebral arteries. It is noted that the internal carotid arteries lie in fairly close relation to the chiasm. In persons in whom the chiasm is located well posteriorly the internal carotid artery may be in close contact with the optic nerve. The internal carotid artery is tortuous in its course and if calcified could exert pressure on the lateral sides of the nerve in some cases and on the chiasm in others.

A diagnosis of calcification of the internal carotid arteries is justified when binasal hemianopsia is present, the roentgenographic examination demonstrates evidence of calcification in the arteries and there are no contravening neurologic signs.

The third case of binasal hemianopsia I have seen was that of a boy 9 years of age, studied at the Neurologic Institute. He had binasal hemianopsia with a defect in the upper temporal fields as well. There was advanced bilateral papilledema, with greatly reduced vision. The outlook was serious, and the neurosurgeons did an exploratory operation, using the transfrontal approach. When the middle fossa was exposed, a cystlike mass, under pressure, was seen compressing the structures anteriorly. The presence of a neoplasm was not confirmed, and biopsy revealed normal brain tissue only. The fluid which was aspirated proved to be normal cerebrospinal fluid. The boy died about three weeks later, of bronchopneumonia, and autopsy revealed an astrocytoma fibrillare beneath the aqueduct of Sylvius. The tumor had grown into the lumen and practically obliterated it. The resulting internal hydrocephalus had dilated the third ventricle, causing the anterior wall to bulge into the chiasmal region. It was believed that the optic nerves were pressed against the internal carotid arteries, with consequent destruction of the lateral fibers of the nerves, thus producing the binasal hemianopsia.

The Paton-Kennedy syndrome may be explained by an expanding lesion which compresses the optic nerve on the ipsilateral side, destroying the fibers and obliterating the subdural spaces. When the lesion has grown sufficiently to produce intracranial pressure, papilledema develops on the contralateral, unobstructed side. No papilledema develops on the side of the lesion because the obliterated subdural spaces prevent the impact of the pressure against the nerve head. The scotoma in the contralateral visual field may be due to a toxin thrown off from the neoplasm or other expanding lesion.

Albright (*Bull. Johns Hopkins Hosp.* 44: 215-245, 1929) reported 31 cases of the syndrome due to aneurysm at or near the circle of Willis in which autopsy was performed. In none had a diagnosis been made during the life of the patient. The third cranial nerve had been involved in each case, the sixth cranial nerve in 19 cases and the superior division of the fifth nerve in 24 cases.

A slide was shown of a drawing after Meyer, published in one of Cushing's papers, to demonstrate the visual centers in the occipital lobes and the optic radiations as they course through the cerebral structures. It is conceivable that there could be a lesion in each temporal lobe which would compress the lateral fibers of the optic radiations or a destructive lesion in each calcarine area, either of which could produce bilateral nasal hemianopsia. However, I have had no personal knowledge

of such a case. Therefore, in the presence of a binasal hemianopsia, one may with reasonable certainty find the lesion in the middle fossa, located in the optic nerve, near its origin, or in the chiasm proper. Lesions of the optic tract are not common, and there are so many vital structures in the immediate proximity that other serious neurologic symptoms exist when the tract is involved. A bilateral lesion is a requisite for the production of binasal hemianopsia. I cannot reconcile the visual fields in this case with an aneurysm confined to one side, and Dr. Igersheimer's explanation does not seem to be altogether satisfying. I should like to ask whether he can further amplify his explanation.

DR. JOSEPH IGERSHEIMER, Boston: I should like to answer Dr. Johnson's question, but I am not able to explain the binasal hemianopsia in this case. I can only repeat what I tried to say before, that the optic nerve on the side opposite the aneurysm was perhaps pressed against an arteriosclerotic artery; arteriosclerosis undoubtedly was present. Or there was perhaps a local nutritional deficiency, so that most of the smaller vessels of the optic nerves and chiasm were in some way pathologic; this is just a hypothesis, however. The latter possibility would be a good subject for investigation, for not much is known about the blood supply. Such a nutritional deficiency would better explain why the visual field of the left optic nerve was regained after the exploratory operation, in which nothing was done, whereas if an arteriosclerotic vessel had been pressing against the left optic nerve it is not clear why the operation should have changed this.

Intraocular Hemorrhage Following Extraction of Cataract. DR. W. C. OWENS and DR. W. F. HUGHES JR., Baltimore.

This paper will be published in full in a future issue of the ARCHIVES.

DISCUSSION

DR. WALTER S. ATKINSON, Watertown, N. Y.: Dr. Owens and Dr. Hughes, in their excellent presentation, have crystallized the views concerning postoperative hemorrhage following cataract extraction.

The low percentage of hemorrhages in the series of cases which they have analyzed is most commendable. In a great measure this can be attributed to operative skill and improved technic. Their suggestion, however, that "the difference in the reported incidence of postoperative hemorrhage is due to variations in definition" is logical. It might explain the low incidence, 7.7 per cent, of hemorrhages in the early cases, in which no sutures were used, as compared with that of 12 to 13 per cent in the series in which conjunctival sutures or one corneoscleral suture was used.

It is my impression that a number of years ago, during the period when sutures were not used, many small hemorrhages were not recorded, as they were considered as of no consequence and apparently did little, or no, harm. Then, too, in the present cases the percentage of hemorrhages for the whole series has unquestionably been lowered by the small number of hemorrhages that have occurred since the adoption of the technic to obtain firm closure with avascular healing.

I hope Dr. Owens will describe the corneal section which he refers to as a shallow one with avascular healing. When such a section is used, are the hemorrhages smaller, with less visual loss?

In my experience of the past few years, the use of a corneal section with firm closure has greatly reduced the amount of bleeding, although the number of postoperative hemorrhages per hundred cases is larger than that in the Wilmer series. This, again, may be partly explained by the "variation in definition" mentioned by Dr. Owens. For some time I have recorded as postoperative hemorrhages all those in which any blood was seen in the anterior chamber at any dressing, since it does not seem practical for each operator to decide which hemorrhages are large enough to record. The notable decrease in the number of hemorrhages, 13.3 per cent, in the group with one corneoscleral suture as compared with the incidence of 4.7 per cent in the group in which two corneoscleral sutures were used is particularly striking. Was the same type of section employed in the two groups?

The authors report hemorrhages following the removal of corneoscleral sutures in 3.6 per cent of their cases, which leaves only about 1 per cent of the hemorrhages in the last series of 558 cases attributable to other causes. If the percentage of hemorrhages following the removal of sutures could be lowered, the problem of postoperative hemorrhage would be near solution.

The conclusion in regard to the influence of general medical conditions as a cause of postoperative hemorrhage is in accord with my experience. Frequently a hemorrhage can be accounted for by a poorly placed section which has been insecurely closed.

In my last 300 consecutive cases of cataract extraction, which include instances of complicated cataracts, there were 34 postoperative hemorrhages. One patient died of a cerebral hemorrhage before leaving the hospital. The others obtained vision of 20/25 or better. Therefore, I have felt that while postoperative hemorrhage is an annoying complication, which may prolong the patient's stay in the hospital, it is not a serious one.

The excellent presentation of Dr. Owens and Dr. Hughes has strengthened my conviction that an accurate and firm closure of a corneal section will practically eliminate postoperative hemorrhage.

DR. FRANKLIN BRACKEN: I have little to add to this excellent paper. I am convinced that firm closure of the wound is the best defense against hemorrhages and that it has greatly reduced them in number and size. Hemorrhage causes no great trouble in my experience, does not greatly affect the vision and seldom makes any difference in the final result. The patient's hospitalization may be prolonged, and staining of the cornea occasionally occurs; but I have seen normal vision eventually result in cases of corneal staining which endured for more than a year.

DR. ARNOLD KNAPP: Drs. Owens and Hughes have made a valuable presentation, for it demonstrates that the cause of hemorrhage is not systemic or general but is a local one which can be present in any type of case; that it can be remedied by an improved operative method is particularly valuable.

DR. CLYDE E. MCDANNALD: I know of surgeons who do a phlebotomy to prevent hemorrhage. I should like to ask the authors whether they performed phlebotomy on any of these patients before operation.

I never saw a case in which that operation was resorted to, but I know of good surgeons who employ it.

DR. W. C. OWENS, Baltimore: Phlebotomy was not performed in any of the cases of this series. There have been reports in the literature on the relation of phlebotomy to the occurrence of postoperative hemorrhage. Carle compared cases of vascular hypertension in which phlebotomy was performed with cases of vascular hypertension in which no phlebotomy was performed. He found no significant difference in the incidence of postoperative hemorrhage in these two groups.

The following technic was employed in the cases with two corneoscleral sutures and is the technic used at the present time. After production of akinesia and a retrobulbar injection, a lid speculum is inserted, and a traction suture is placed in the superior rectus muscle. An incision for a conjunctival flap, measuring 3 to 4 mm., is made from 3 to 9 o'clock and carried down to the limbus to the point of transition between conjunctival and corneal epithelium. This point is about 1.75 to 2 mm. from the root of the iris. A partial incision is then made halfway through the thickness of the limbus at an angle of 10 to 15 degrees from the perpendicular. Into this partial incision are placed two corneoscleral sutures, at 1 and 11 o'clock: A Graefe knife is used to make the section, which comes out in the base of the partial incision previously made. The necessity that the Graefe knife follow the partial incision, carefully placed beforehand, insures a section in the exact position desired—well forward in relatively avascular tissue.

In the cases with conjunctival sutures and in a few cases with only one corneoscleral suture, the sections were more posterior, and therefore in more vascular tissue.

Rudolf Aebli, M.D., *Chairman*

Truman Boyes, M.D., *Secretary*

April 15, 1946

INSTRUCTION HOUR

Wrong Glasses From the Right Prescription. MR. AUREL E. MANGOLD.

In this discussion the speaker stressed the importance of proper fitting of ophthalmic lenses, explaining how and why improper adjustment may impair the results of an expert refraction. He dealt with correct methods of measuring interpupillary distances, compensation for vertical imbalances in anisometropia, vertex distances and their effects on lenses for cataract and on high corrective lenses. He also included consideration of the importance of lens forms as related to aniseikonia; mechanical factors and difficulties encountered with lenses for aphakia and high dioptric prescriptions, and critical factors in the selection of lenses for such conditions. The use of the lensometer, the lens clock and neutralization as methods of checking finished lenses and the analysis of lens forms in relation to the patient's refractive errors were emphasized. A suggested routine for checking lenses, by themselves and in their relation to the patient and his symptoms, was also presented.

REPORTS OF CASES

"Soft Glaucoma" and Calcification of the Internal Carotid Arteries.
Dr. John M. McLean and Dr. Bronson S. Ray.

This paper will be published in full in a future issue of the Archives.

DISCUSSION

Dr. Bronson Ray: It is all very well to suggest a possible mechanism for this ophthalmologic problem. We should be much more gratified to be able to suggest something to do about it. The rather difficult situation in the case we presented, and in others like it, is obvious. Yet it may be that there is something to be accomplished by a procedure which we hope we may try at another time, namely, the decompression of the optic nerve in its canal by removal of the roof of the canal. In a situation such as Dr. McLean has shown the nerve is virtually held immobile as it enters its canal, and at that very point it receives its greatest insult from the artery. Theoretically, it seems to me if one could unroof the canal and let the nerve be displaced upward it might have a better chance of survival in the circumstances. This, I realize, is complete speculation, and perhaps unwarranted wishful thinking. However, if ophthalmologists are to be enthusastic in finding a cause for conditions such as this, they ought to show a little more enthusiasm in doing something about it.

Dr. Arnold Knapp: The authors' case corresponds to those described in the older literature as instances of atrophy of the optic nerve of arteriosclerotic origin (Otto, R.: Untersuchungen über Sehnervenveränderungen bei Arteriosclerose, Berlin, Julius Springer, 1893). This was before the days of roentgen rays, and the diagnosis was made at necropsy. On the other hand, the cases which are now associated with sclerosis of the basal arteries are, I think, different. The altitudinal field defect, while characteristic, is not always present; the cupping of the optic nerve is distinct, and the intraocular tension is always low. Calcification of the basal vessels is not always recognizable on roentgenologic examination, but a vascular disturbance of the optic nerve is assumed to be present in all cases.

Dr. Wendell L. Hughes: May I ask Dr. Ray whether he thinks it might be possible to unroof the canal of the optic nerve and insert fascia around the carotid artery in that area, introducing it between the artery and the nerve, in order to cushion the shock of the pulsation of the artery against the nerve?

Dr. Clyde E. McDannald: I should like to ask whether any method is known which can be employed in decalcification in these cases. I ask this because I had in my office this morning a man who came first with disciform keratitis. Now, after three or four weeks, he has a spider-like opacity, and it looks very much like a calcification. He said that he had had two calcified nodes removed surgically from his elbows and asked whether there is any method of treatment which will remove calcified areas from the body.

Dr. Bronson Ray: The optic nerve canal is a rather confined place in which to work, and one is continually aware of the danger of traumatizing the nerve by undue manipulation. Even removal of the roof

of the canal might be fraught with hazard. But if a piece of fascia were to be introduced between the vessel and the nerve, it might counteract whatever benefit would accrue from releasing the nerve; in other words, the fascia might take up more space than was justified.

DR. JOHN MCLEAN: Dr. McDannald, I do not pretend to be a chemist or an authority on decalcification, and I think I had better not answer your question.

In reply to Dr. Knapp's comments: I was impressed, on reviewing his two papers on the subject, by the extreme similarity of the clinical pictures and the great similarity of the visual fields in my case and in the cases which he originally reported, particularly those in his first paper. Of course, the operative observations were very different from those to be expected from his roentgenograms; but we have an equal basis for comparison. I carefully compared the fields in my case with field after field in the 10 cases Dr. Knapp reported, and I was impressed, not by the differences, but by the similarity. With regard to cupping of the optic nerve and the diagnosis of pseudoglaucoma, I should like to say again that this patient was examined, and the diagnosis of pseudoglaucoma, or "soft glaucoma," made, by a fair number of ophthalmologists, over a dozen, some in this city and some in places outside New York; there was a slightly smaller number who disagreed with the diagnosis, but the disks resembled closely enough the picture of pseudoglaucoma to suggest the diagnosis to so many.

Lipemia Retinalis. DR. F. L. PHILIP KOCH (by invitation) and DR. PAUL S. STRONG (by invitation), New York.

This paper will be published in full in the ARCHIVES.

DISCUSSION

DR. LUDWIG VON SALLMANN: I should like to ask Dr. Koch whether he considers examination under red-free light of value in the diagnosis of retinal lipemia, since a granular current in the retinal vessels may be detected with this method in an early stage of the condition.

DR. F. L. PHILIP KOCH: With regard to Dr. von Sallmann's question concerning examination under red-free light, we have not made such a study. It did not occur to us to study the eyegrounds from that point of view or to determine the appearance of the fundi under red-free light. The contrast was much more striking with respect to the lack of coloration than it was at a later date; that is, it was much more striking at first than when the color returned more nearly to normal.

Ophthalmoscopic Changes Associated With Essential Hypertension as a Guide to Sympathectomy. DR. MARTIN COHEN.

The paper will appear in full in a future issue of the ARCHIVES.

DISCUSSION

DR. HERMAN O. MOSENTHAL: We have heard the opinions of one of the wisest of all ophthalmologists on a timely subject. He finds that sympathectomy relieves many of the changes in the fundus occurring

with essential hypertension. The close observation of 90 patients before and after operation, during their long period of hospitalization, is an arduous task, and we are greatly indebted to Dr. Cohen for the valuable records he has assembled.

Many internists and ophthalmologists have stressed the idea that the retinal lesions are the most important sign of hypertension, as a guide both to therapy and to prognosis. It is with gratification that I quote Dr. Cohen: "A definite prognosis is not possible from the findings in the fundus alone, as the prognosis may be influenced by pathologic changes in other organs." Considering that 60 per cent of the many patients with hypertension die of cardiac failure and that only a comparative few suffer visual impairment, the truth of Dr. Cohen's statement is apparent.

Also, I agree with Dr. Cohen that the eyegrounds are the best visible guide to the condition of the systemic blood vessels. There can be no doubt of the truth of that statement. However, of 22 patients with normal fundi in Dr. Cohen's series, biopsy revealed normal kidneys in only 3, while 19 had nephrosclerosis. The pathologic condition of the kidneys, therefore, is often a more delicate index of the effects of hypertension than is the appearance of the retina.

With these reservations in mind, let us look at the positive indications. Dr. Cohen's' observations show that retinal hemorrhages, exudates and vasospasm will disappear after sympathectomy. This fact is of great value as a guide to the advisability of performing sympathectomy. In some instances hypertension exerts its influence on the retina in a selective, devastating fashion. Such lesions may be relieved by sympathectomy.

Dr. Hinton performed sympathectomy in 2 young men who were incapacitated through loss of vision. They were both nephritic. One had normal renal function; in the other the urea nitrogen of the blood was distinctly raised. Nephritis is considered a contraindication to the performance of sympathectomy. However, the operation resulted in complete restoration of vision in these 2 patients. They were able to resume work, one as a railway express clerk and the other in a defense plant. Within about a year coronary thrombosis and uremia closed the picture for these men. Nevertheless, one year of untrammeled living was surely worth the price.

The strain imposed on the arteries and arterioles by the hypertension is the cause of arterial and arteriolar changes. The resulting vasospasm, hemorrhages and exudates are reversible, while arteriosclerosis is not, as has been stressed by Dr. Cohen. Favorable effects come about whenever the blood pressure is lowered. The question arises: What is the most successful method of reducing arterial hypertension? Dr. Cohen has mentioned that sedation and rest often accomplish a great deal. I hope that the title of this paper does not imply that sympathectomy is the method of choice. This operation, to my mind, is distinctly in the experimental stage and is far from being a panacea for the hypertensive state.

I recall the disfavor incurred by those of us who were skeptical about the value of nephro-omentopexy and the use of renal extracts. I trust that the unbelievers may be proved wrong, but for the present

I am among those who are doubtful as to the wisdom of the extensive application of sympathectomy in cases of hypertensive disease.

I shall cite the results in 3 cases of hypertension to show that there is no single formula for success in the treatment of this disease and that improvement in the fundic changes and lowering of the blood pressure may be achieved by many different means.

A minister, aged 43, was seen in May 1929. He was said to have a hopeless case of uremia. He was weak to the point of exhaustion. The blood pressure was 190 systolic and 120 diastolic, the hemoglobin 54 per cent, the red blood cell count 3,110,000 and the urea nitrogen content of the blood 38 mg. per hundred cubic centimeters. Vision was impaired because of retinitis. The malnutrition had been engendered, in part at least, by a low protein diet. He was given three transfusions totaling 2,500 cc. of blood and was allowed a high protein diet. After this treatment the blood count became normal; the blood pressure dropped to 154 systolic and 100 diastolic; the retinitis disappeared and vision was restored; his energy revived, and he resumed preaching and attended football games. Presumably, his tissues had been injured by semistarvation. Proper nutrition reversed his condition in many respects. Two and one-half years later there was an exacerbation of the hypertension, and he died of cardiac failure. This record is fully as good as those of the 2 patients with nephritis subjected to sympathectomy previously cited.

A housewife aged 58 had loss of vision because of hemorrhagic retinitis associated with severe diabetes and a blood pressure of 238 systolic and 140 diastolic. Control of the diabetes, complete rest in bed and a low caloric diet promoted absorption of the hemorrhages. Six months later vision was again impaired because of recurrence of the retinal hemorrhages. The same measures were again effective. The blood pressure remained constantly high. Thorough relaxation and an antiobesity diet proved satisfactory in this case, the direct opposite of the therapy used in the first case.

Mrs. M., a teacher aged 42, on Dec. 8, 1945 had a blood pressure of 196 systolic and 128 diastolic; one week later it was 194 systolic and 124 diastolic. The blood pressure seemed to be permanently elevated. Within another week the blood pressure dropped to 166 systolic and 110 diastolic and subsequently to 136 systolic and 94 diastolic, at about which level it has remained for four months. She has kept on with her exacting work and is subject to inescapable home worries. In addition to an antiobesity diet, resulting in a loss of weight of 26 pounds (11.8 Kg.), symptomatic medication was prescribed. How such a result was accomplished I do not know, but the fact remains that gratifying changes in blood pressure were achieved by simple means, without resort to specific remedies or operation.

DR. J. WILLIAM HINTON: I am at a loss in discussing this paper because I can agree with some of the points that Dr. Cohen has stressed, one of which is, if I understood him correctly, that the changes in the fundus are perhaps the best guide in selection of patients who will respond favorably to thoracolumbar sympathectomy, and another guide is in the grouping of these ocular changes. I am ready to admit that I am not competent to evaluate changes in the fundus and have to take the opinion of those who really know. It will be recalled that 23 of the patients in Dr. Cohen's series were reported normal; the cases in this series do not represent consecutive cases; they represent only 90 cases out of about 250 in which operation was performed. Some of the patients had complete ophthalmologic studies before their entry

into the hospital, and they were not restudied; so Dr. Cohen's series represents to a certain degree a cross section of the larger group. The normal findings in the fundus are upsetting, for I can assure you that, aside from the eyes, these patients were far from normal, and that in itself is confusing in selecting patients with respect to the seriousness of the operation. Recently I saw a patient who had had two attacks of coronary disease. She had been treated by an excellent cardiologist, and he felt that she should have an operation. She was normal in every other sense and had recovered from the coronary disease. Her eyegrounds were of group 1 type, and she felt that for this reason she was a safe risk. From my point of view, it is dangerous to operate on a patient who has had two attacks of coronary thrombosis, and if one relies on the eyegrounds one will be misled as to the underlying arteriolar sclerosis in the brain, coronary arteries and kidneys. The good results speak for themselves; the difficult thing is to evaluate the failures, and it is very interesting to correlate all the data available in order to decide on whom to operate and whom to exclude. The over-all mortality for the 227 patients operated on during the past four years, which means the mortality for patients in and out of the hospital to date is 26, or 11.5 per cent. Using the classification of Keith, Wagner and Barker based on the eyegrounds, one finds that 30 per cent of group 1 are dead in three years, and at the end of six years the mortality is still only 30 per cent. For group 2 the mortality is 38 per cent for three years and the same for five years. For group 3 the mortality is 78 per cent after three years, and for group 4 it is 94 per cent. It is obvious that the patients in groups 3 and 4 have had serious organic disease, in the heart, cerebral vessels or kidneys. This gives an index as to what will happen to patients falling in group 4. My colleagues and I have 20 patients in group 4 who have been operated on and followed for six months to three years. Eleven are alive and well, a proportion which compares favorably with the figures of Keith, Wagener and Barker.

In Dr. Cohen's series, 23 of the patients had normal eyes and 43 mild changes; that means that 73.3 per cent of the 90 patients had minimal ocular changes, but 80 per cent of these patients were actually critically ill with advanced essential hypertension. Hence, the eyegrounds are obviously of little aid in selection of hypertensive patients, both as to their ability to stand operation and as an index as to the prognosis after operation. One can be misled if one follows the findings in the eyegrounds too literally. In reviewing the failures, I have found some interesting figures. Perhaps the most accurate clinical information is obtained from the sodium amytal test. That test must be done accurately. One cannot have one resident doing a few tests and another a few and rely on the results. For the past fifteen to sixteen months we have had a nurse technician doing nothing but these sodium amytal tests, and the results are fairly accurate: we have found that the patients whose diastolic pressure does not fall below 100 are the ones in whom we will get poor results. For practically all patients whose diastolic pressure falls below 100 the results have been satisfactory, with practically no deaths in or out of the hospital. That, from the surgical point of view, is most important; it means one has an index in selection of these patients.

In spite of the knowledge that the internists have, they cannot exclude some of the patients who have early renal disease. The urea clearance and concentration tests are satisfactory; the blood chemistry may be normal, but uremia develops, with a urea nitrogen value of 60 to 70, or even 100, mg. per hundred cubic centimeters and a creatinine of 10, 12, 15 or 16 mg. and a nonprotein nitrogen value which is much bigger. So far as I have been able to see, there is no satisfactory test that will rule out early renal disease. It is obvious that if the surgeon knew there was so much renal damage he would not operate. Patients with severe renal damage will not be helped by thoracolumbar sympathectomy. After one analyzes all the data, from the renal function tests, the electrocardiograms, etc., one is still in a quandary as to whether the patient will stand the operation and, if he stands it, whether the result will be good.

We have classified patients as those who were 50 years of age and those who were older. Some of the best results we have had were in persons over 50. Of 34 patients above 50, 2 were over 60 and 7 were between 55 and 60, and in two thirds of this group the results were good.

Twenty-four patients had type 4 changes in the eyegrounds. If one other organ is seriously involved, that is, if there is severe cardiac, renal or cerebral damage with type 4 changes in the fundus, there is a 50:50 chance of improvement. Of 4 patients with changes in the eyegrounds of type 4 with no evidence of involvement of any other organ, all improved. If the patient has two organs involved other than the eyes, he has little chance of being helped by sympathectomy. We found that of 74 patients with one organ involved and fairly extensive changes in the eyegrounds, 50 were notably improved. Twenty-six patients died, and of these, if the changes in the eyes, kidneys, heart and brain are evaluated on the basis of + to + + + +, with a total of 16 + + + + grades, it was found that 15 patients had 12 + + + + grades out of 16 such grades, and those patients should not have been operated on. The other patients who died had from 8 to 5 + grades or less, and operation seemed indicated.

The clinical impression I got from these patients is that the patients with encephalopathy do the worst. I am not speaking of persons who have had strokes; some of them do very well; I mean the patients who have had a period of unconsciousness of three to five minutes; or they are irritable; they grope for words; their memory is poor, which means they have fairly advanced cerebral arteriolar sclerosis, and we have found this group of patients, although they may have good renal function and good electrocardiograms, are the ones who will die of a cerebral thrombosis or hemorrhage.

To sum up: The eyegrounds are definitely an aid in selection of patients, but they represent only one phase of the problem. Seventy-six per cent of the patients in this series had histologic evidence of renal disease. It is evident, then, that the renal disease precedes arteriolar changes of the retinal vessels when, according to Dr. Cohen's observation, 73.5 per cent had minimal changes or normal eyegrounds.

DR. FRANK A. VESEY: It was a pleasure to listen to these excellent presentations, and I enjoyed most those of Dr. Cohen and Dr. Mosenthal. Dr. Hinton presented his views ably, and they can be discussed with

the papers of the other two. I was glad that Dr. Cohen did not choose to discuss the Wagener-Keith-Barker classification. No matter how fashionable it is today, it is rather artificial, looked at from the ophthalmologic angle. The first two groups can well be interpreted as normal, and I am glad that Dr. Cohen spoke of mild, moderate and severe changes and of malignant hypertensive retinopathy.

Dr. Cohen pointed to an artery on one of his slides, saying that this artery, although attenuated, cut in two the underlying vein. Such arteries are not really attentuated; in fact, they are thickened. But hyaline degeneration and thickening do not always make the arterial walls visible. In most cases they remain entirely transparent, and the arteries seem attentuated on account of the narrowed lumen. The underlying vein seems interrupted by the concealment.

As to the merit of sympathectomy, I think it should at best be regarded as palliative treatment. I have seen cases in which there was no beneficial result and others in which there was temporary subjective improvement, but I was not lucky enough to see, or even to read about, one in which an unbiased observer could testify to a real, substantial improvement.

Dr. Cohen says that the fundus picture is a good indicator of the real condition of the patient. Dr. Hinton does not believe that this is so. I think most of us here agree with Dr. Cohen. If the underlying hypertensive disease is severe enough to cause visible changes in the retina, the other organs, especially the kidneys and the brain, will invariably present changes of an even greater degree—so much so that if a definite retinopathy is visible and can be so diagnosed the life expectancy of the patient is not more than three years. Of course, some such patients may go on longer, but others will fall victim to a cerebral catastrophe or uremia much sooner.

Dr. Hinton said that the best patients for operation are those who display no retinopathy. These are the patients who can carry on for decades with general medical treatment, and sympathectomy is superfluous.

Dr. F. L. Philip Koch: Dr. Cohen has presented this subject interestingly. I wish to ask him several questions concerning basic intraocular physiology and pathology. Does he believe that there exists any justification for retention of the term "tortuosity" with reference to the retinal arterioles in hypertensive disease? Does he recognize the dynamism inherent in the progression of hypertensive disease from normality through the alterations attendant on abnormal vascular physiology of the arterioles to the progressive phases of organic arteriolar changes, represented ophthalmoscopically by the so-called copper wire and silver wire appearance? Does he recognize that statistical evaluation of postoperative data on occasion has been conducted with more enthusiasm than objectivity and that it has failed to recognize the importance of the degree, or intensity, not only of the attenuation of retinal arterioles but also of the sclerosis, as well as its origin?

It will be recalled that in the early days of ophthalmoscopy the indirect method frequently was used, but even the most careful observers failed, under the standards of illumination then prevalent, to distinguish sufficiently between the pathologic vascular alterations of one entity as

compared with those of others, as they are known today, to assist the internists in differentiating any one hypertensive syndrome complex from any other. This statement does not hold true uniformly, but its basic accuracy is attested by the retention, even today, of the term albuminuric retinitis" in some communities in this country and elsewhere. This term, although no longer in reputable use, is one of the numerous hold-overs of nomenclature of an earlier period, during which it came to be recognized that "cardiovascular-renal" disease was not a single disease but represented a clinical *pot pourri*, which was comprised of many ingredients in almost infinite combination.

The concept of arteriolar, in contradistinction to arterial, physiology and pathology gradually gained supporters. The occurrence of atheromatous changes elsewhere than in the great vessels was recognized, and its importance was established in geriatrics. It was acknowledged that there existed a difference with respect to a man's usefulness as a citizen and his life expectancy on an actuarial basis and that differentiation must be made between the chronic and the more severe phases of vascular disease, particularly with reference to hypertensive disease. Ophthalmoscopic diagnostic criteria tended to become increasingly important, but these could not be accorded their full stature unless, and if, some of the earlier phraseology was discarded. "Tortuosity," for example, is a term that should be used with great care. It implies a decrease in elasticity of the arteriolar and arterial walls. This is provable in the laboratory. On the other hand, it connotes a diminution in the ability of the wall to undergo constriction. Perusal of the older literature will reveal the fact that indirect ophthalmoscopy accentuated whatever waviness of the vasculature was present. Many of the very early observers, who, a half-century before the routine use of the sphygmomanometer, tended to believe that cardiovascular-renal disease was simply cardiovascular-renal disease, understandably were somewhat responsible for the terminology that many ophthalmogists still use in describing the eyegrounds. It is this unfortunate tendency to overlook the basic reasons for the pathologic changes observed that leads many ophthalmologists to cling to descriptive terminology that no longer has any modern clinical usefulness, except in a historical-descriptive sense. It is the same tendency, deplorably, that militates against consistently accurate interpretation of changes in the eyegrounds that we observe.

It is especially important that interpretations be as accurate as possible when one is determining whether to advise a patient to undergo surgical treatment for the relief of essential hypertension. It has been shown by Wagener and his group and by others that in the main the less intense the arteriolar sclerosis in a patient with established hypertension, the more likely is he to derive benefit from sympathectomy, and the more advanced the sclerosis, the less likely is he to obtain relief, although severe cephalgia probably will decrease in approximately one third of all cases. It is unreasonable to suppose that sympathectomy will be beneficial where generalized atheromatosis has coexisted with essential hypertension or has been present prior to the onset of increased diastolic systemic blood pressure.

DR. MARTIN COHEN: I have examined about 34 patients with malignant essential hypertension with all the clinical manifestations and have studied sections of autopsy material, including serial sections; and

in most cases I found malignant nephrosclerosis. Malignant nephrosclerosis is a pathologic diagnosis. In cases of neuroretinopathy with edema of the disk, even partial edema, and increased pressure, one will find pathologic evidence in the kidney of malignant nephrosclerosis; all the blood vessel walls will be fibrillated; the lumen of the vessels will be encroached on, and the lastica will be separated and split. Since in cases of malignant essential hypertension, with or without papilledema, the kidney shows malignant nephrosclerosis, I think the term malignant essential hypertension with or without papilledema should be included in the diagnosis. In one of the articles cited a case of malignant hypertension with neuroretinopathy was described.

In regard to the case of atherosclerosis of which Dr. Hinton speaks, the lesion is not arteriolar; it affects the larger blood vessels, such as the aorta or some of the cerebral basilar vessels, where one sees plaques; no plaques are seen in any arteriolar vessel.

News and Notes

GENERAL NEWS

Howe Lecture in Ophthalmology.—Prof. William John Brownlow Riddell, fellow of the Royal Faculty of Physicians and Surgeons, and dean of medicine at Glasgow University, will give the Howe Lecture in Ophthalmology on "Heredity and Variation in Clinical Ophthalmology" at the Harvard Medical School on Tuesday, Nov. 19, 1946.

Book Reviews

The Fundamental Colour Sensations in Man's Colour Sense. By Gustav F. Göthlin. Pp. 76, with 21 illustrations in black and white. Uppsala: Almquist & Wiksells, 1943.

This monograph, which is the authorized English translation of the original treatise in Swedish, will appeal to the student of color vision and color vision theory more than to the ophthalmologist. It includes a report on experimental work previously published by the author which deals with color responses particularly in the yellow and indigo regions of the spectrum. These data, together with historical and critical observations, form the framework of Göthlin's thesis that the fundamental color sensations in man's color sense are red, green and blue; that yellow and violet are not fundamental colors—points of controversy since before the days of Thomas Young. A fundamental color sensation is defined by Göthlin as the sensation that would be produced by any one of the retinal processes alone, assuming it could occur alone.

Yellow, he contends, is a sensation arising from the simultaneous effect of impulses from the receptors for red and green. This conclusion is drawn from his experiments which show that the position of pure yellow in the spectrum varies among persons having normal trichromatic vision, that the range of pure yellow in the spectrum is very narrow and that there are individual differences in the Rayleigh equation which are not satisfactorily explained by assuming individual variation in macular pigment. These phenomena are best explained by assuming (page 10) "an individually varying proportion of the number of receptors for red and for green." As further evidence against the supposition of yellow as a fundamental color he cites the binocular fusion of red and green to give yellow (claimed by Hering and Trendelenburg, denied by Rochat) and the extraordinary narrowness of the spectral zone for yellow shown in hue discrimination curves.

Violet, the author contends, is a sensation arising from the simultaneous effect of impulses from the receptors for blue and red. He reviews critically previous arguments in favor of violet as the short wave fundamental color, which were based mainly on color mixture data and studies of the color vision in cases of congenital tritanopia. From his detailed analysis of these rare cases of defective color vision, Göthlin concludes (page 67) "that they belong to two categories. The cases belonging to one group are blue-blind but have colour sensations from the violet part of the spectrum. Those belonging to the second group are both violet and blue-blind. In the latter group a simultaneous weakening in the perception of long-wave red was observed." To the reviewer, this section of Göthlin"s book is the most interesting. Reported cases of congenital tritanopia are few and not readily accessible. This compilation has therefore considerable value.

The author's experimental evidence in favor of blue and against violet as a fundamental color is based on his attempt to separate the

blue and red components in violet in persons with normal color vision. A series of experiments on the threshold energies for the appearance of color in spectral light of wavelengths ranging from 430 to 460 millimicrons shows that for most of his observers the color was first identified as blue. Only with greater energy of light was the red component identified. No observer reported an appearance of violet or green prior to the appearance of blue. Göthlin concludes (page 67) "that blue must have its own receptors and be a fundamental colour, but that indigo—in one case also proved for violet of wave-length 425 mu. —arises from the fusion of impulses from blue and red receptors."

Considerable space is devoted to the development of Göthlin's three component theory, based on red, green and blue as fundamental colors. He holds (page 70) "that every impulse from the retinal receptors to a colour sensation is necessarily combined with a certain degree of central inhibition of the complementary colour in the same area, the degree of this inhibition being bounded by a certain law." Red plus green yields yellow and yellow plus blue yields white, by a mechanism taken to be an inhibitory action in the central nervous system. The theory is illustrated with a compound balance model. While containing elements derived from the classic Young-Helmholtz and Hering theories, his thesis is most reminiscent of the Ladd-Franklin theory (1892), although the similarity is not mentioned by him.

GERTRUDE RAND.

Collected Reprints from the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. July 1942-July 1945. Volume 7. Pp. 134. Baltimore, 1945.

The reprints of the articles written by members of the Wilmer Ophthalmological Institute during the period from July 1942 to July 1945 have now been collected in a bound volume, making volume 7 of the series. There are 61 titles of reprints and 6 titles of articles not reprinted in this volume.

The articles treat a large variety of subjects, which represent additions to knowledge in practically every branch of the now broadening field of ophthalmology and are witness to the interest and industry of the members of the Wilmer staff, under the stimulating guidance of their director.

ARNOLD KNAPP.